ACUROX®

(oxycodone HCl, USP and niacin, USP)

Tablets

NDA 22-451

Briefing Information for a Joint Meeting of the
Anesthetic and Life Support Drugs Advisory Committee
and
Drug Safety and Risk Management Advisory Committee

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Acura	Acura Pharmaceuticals, Inc
AE	Adverse event
Agency	U.S. Food and Drug Administration
ARCI	Addiction Research Center Inventory
AUC	Area under the plasma concentration versus time curve
AUE	Area under the effect versus time curve
C_{max}	Maximum plasma concentration
CFR	Code of Federal Regulations
DRQS	Drug Rating Questionnaire – Subject
ED	Emergency Department
$E_{0.5}$	Disliking effect at 30 minutes post-dose
E_{min}	Peak (maximum) Disliking Effect
ER	Extended-release
FDA	U.S. Food and Drug Administration
HCl	Hydrochloride
HIV	Human Immunodeficiency Virus
IIG	Inactive Ingredient Guide
IR	Immediate-release
ITT	Intent-to-Treat
IV	Intravenous
LSD	Lysergic Acid Diethylamide/Dysphoria Scale
MBG	Morphine-Benzedrine Group/Euphoria Scale
NDA	New Drug Application
NSAIDs	Non-steroidal anti-inflammatory drugs
PCAG	Pentobarbital-Chlorpromazine-Alcohol Group/Sedation Scale
PI	Pain intensity
PK	Pharmacokinetic(s)
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance System
RLD	Reference Listed Drug
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error of the mean
SKIP	Survey of Key Informants' Patients
SPID	Sum of Pain Intensity Difference
SVAQ	Street Value Assessment Questionnaire
TDAA	Take Drug Again Assessment
T_{max}	Time to maximum plasma concentration
TEAE	Treatment-emergent adverse event
TEAQ	Treatment Enjoyment Assessment Questionnaire

TRS	Tolerability Rating Scale
US	United States
USP	United States Pharmacopeia
VAS	Visual analog scale

1.   EXECUTIVE SUMMARY

1.1   Introduction

Acurox® (oxycodone HCl/niacin) Tablets are an immediate-release (IR) combination product containing 2 active ingredients and an essential composition of functional inactive excipients. Each Acurox® Tablet contains oxycodone HCl as the sole active analgesic ingredient. Niacin, the second active ingredient, is intended to minimize the potential for oral abuse of oxycodone HCl. Both oxycodone HCl and niacin are FDA-approved drugs with extensive clinical experience and well characterized safety profiles. The unique mixture of functional excipients in Acurox® Tablets are designed to minimize the potential for intranasal and intravenous abuse. The proposed indication for Acurox® Tablets is for the relief of moderate-to-severe pain where the use of an immediate release, orally administered, opioid analgesic tablet is appropriate. Acurox® Tablets are designed to relieve moderate-to-severe pain and minimize the potential for opioid abuse by the 3 most common methods including; oral (when taken at doses higher than recommended), intranasal (nasally snorting crushed tablets) and intravenous (IV) injection of dissolved tablets).

Acurox® Tablets were shown to be effective in relieving moderate-to-severe pain and were well tolerated in an adequate and well-controlled clinical study in 405 patients with post-operative pain. In addition, abuse liability studies in over 100 recreational opioid abusers and laboratory studies demonstrated the ability of Acurox® Tablets to provide limits or impediments for the 3 most common methods of opioid abuse.

Based on review of these studies submitted in the new drug application, FDA issued a Complete Response Letter which questioned the incidence of flushing in pain patients and the relative effectiveness of niacin to minimize the potential for oxycodone abuse. The objective of this briefing document is to review the results of studies evaluating the inclusion of niacin in Acurox® Tablets for the purpose of reducing the misuse and abuse of oxycodone.

1.2   Misuse and Abuse of Immediate-Release Opioids

Immediate-release opioids are an important contributor to the growing public health dilemma caused by misuse, abuse, and diversion of prescription opioid analgesics. It is estimated that the societal costs of prescription opioid abuse totals approximately $50 billion annually. The availability of IR opioid analgesic products in the United States (US) is significant. In 2009, 254 million prescriptions were dispensed, of which 238 million (approximately 94%) were for IR opioids. Opioid analgesic abuse results in a staggering number of emergency department visits, addictions, and deaths each year.

Abusers have been categorized into three main groups: (a) novices/experimenters typically administer opioids at varying and increasing oral doses, (b) established non-dependent abusers who take opioids for recreation more frequently, at higher doses, and may progress to nasal and even IV administration and (c) addicts who are most likely to manipulate the drug products into a solution suitable for IV use.

Oral ingestion of prescription opioids is the most prevalent method of misuse and abuse. It is the method preferred by novices and experimenters. The oral route of administration also results in the highest number of deaths. Legitimate pain patients can misuse opioid analgesics by over-medicating, or using them non-medically. Over-medicating occurs when

the patient takes more of the drug than prescribed by their physician to treat pain. Non-medical use occurs if the patient uses the drug for its psychoactive effects. Prescription opioid abuse for non-medical purposes represents the greatest proportion of abuse.

The FDA has stated that medicines that incrementally address the misuse, abuse, and diversion of currently available opioid drugs would be expected to have public health benefits. In the absence of a perfect solution, and as an incremental step forward, one approach that has been encouraged by FDA and other government agencies is the development of opioid products which introduce some limits or impediments to abuse as opposed to the outright elimination of abuse. The development of Acurox® Tablets is an example of such an approach.

1.3   Acurox® Tablets

The objective of the Acurox® Tablets program was to develop an IR opioid analgesic product that:

1) safely and effectively relieves moderate-to-severe pain;

2) minimizes the potential for oral, intranasal, and IV abuse of IR oxycodone HCl; and

3) substantiates via clinical and laboratory studies a reduction in the potential for abuse, thereby providing an incremental benefit over existing commercially available IR oxycodone products.

Two strengths of Acurox® were developed:

1) Acurox® (oxycodone HCl/niacin) Tablets 5/30 mg.

2) Acurox® (oxycodone HCl/niacin) Tablets 7.5/30 mg.

1.4   Niacin in Acurox® Tablets

Niacin, the second active ingredient in Acurox® Tablets, is an approved drug and is widely used as a lipid lowering agent and in over-the-counter vitamins and food supplements. Niacin has a well-established safety profile at doses many times greater than the 60 mg contained in the recommended 2 tablet dose of Acurox® Tablets, and even many times greater than the amount of niacin likely contained in an abused dose of Acurox®.

Importantly, however, the Acurox development program has established that niacin produces disliking effects when Acurox® Tablets are swallowed in excess doses. Niacin was determined (through 3 niacin dose-ranging studies) to be generally well tolerated at doses of 90 mg or less, with less well tolerated effects manifesting at doses of 120 mg and increasing in severity in proportion to the dose. Based on these results, 30 mg of niacin was added to each Acurox® Tablet.

At the recommended 2 tablet dose of Acurox® Tablets in 269 pain patients, the incidence of flushing was 11% to 16% (placebo was 1.5%). Flushing symptoms were generally mild and transient, posed no safety concerns, and were clinically benign. There were no reports of serious adverse events (AEs) and no subject discontinued participation in the clinical trial as a result of flushing at proposed recommended analgesic doses.

1.5 Acurox® Tablets Development Program

The development program for Acurox® Tablets comprised 11 clinical trials: 1 pivotal safety and efficacy study in patients with moderate-to-severe pain; 3 oral abuse liability studies in recreational opioid abusers; 1 intranasal abuse liability study in recreational opioid abusers; 3 safety/tolerability studies in healthy subjects; and 3 pharmacokinetic and bioequivalence studies in healthy subjects.

1.5.1 Analgesic Efficacy

The analgesic efficacy and safety of oxycodone HCl is well established through decades of clinical use. However, a randomized, double-blind, placebo-controlled, multicenter, repeat-dose pivotal efficacy and safety study in 405 bunionectomy patients confirmed that 2 dose levels of Acurox® Tablets (10/60mg and 15/60mg) provided statistically significant pain relief ($p \leq 0.0001$) compared to placebo. The primary endpoint was the sum of pain intensity differences measured over 48 hours ($SPID_{48}$) using a 100 mm visual analog scale (VAS). These results were supported by key secondary efficacy variables.

1.5.2 Abuse Liability Studies

There is an evolving body of literature concerning study design and methodology for assessing abuse potential which has been published over the past few decades, and has helped FDA in preparing a Draft Guidance for Industry entitled "Assessment of Abuse Potential of Drugs" issued in January of this year and is in the public comment stage. Key elements of the draft Guidance were included in all of the abuse liability studies conducted with Acurox® Tablets.

1.5.2.1 Oral Abuse Liability

Three (3) double-blind oral abuse liability clinical studies enrolling over 100 non-dependent, recreational opioid abusers demonstrated, through the primary like/dislike measure, that Acurox® Tablets, when swallowed in excess oral doses, were significantly disliked ($p<0.05$) at 30 minutes post dose compared to equivalent doses of oxycodone HCl alone (with no niacin). In addition, excess oral doses of Acurox® Tablets caused significant somatic discomfort compared to oxycodone HCl tablets alone. The results were corroborated by the Take Drug Again Assessment (TDAA) or the Treatment Enjoyment Assessment Questionnaire (TEAQ). When given a choice on the TDAA and TEAQ questions, the recreational drug abusers significantly preferred to take oxycodone HCl tablets again compared to Acurox® Tablets. The TDAA/TEAQ may be considered surrogate measures used in clinical studies that are known to correlate with real-world behavior. These 3 clinical studies support the conclusion that Acurox® Tablets may have a lower potential for oral abuse than oxycodone HCl tablets without niacin.

The symptoms induced by niacin may be mitigated by food or non-steroidal anti-inflammatory drugs (NSAIDs). These niacin mitigation effects vary by subject and are not always complete. Data from one of the Acurox® oral abuse liability studies indicated that niacin-induced disliking of oxycodone HCl may be partially mitigated by a high fat meal. Knowledge and advanced planning on the part of a prospective abuser is required to thwart the disliking effects induced by excess oral doses of Acurox®.

1.5.2.2   *Intranasal Abuse Liability*

A randomized, single-blind, clinical study in non-dependent, recreational opioid drug abusers demonstrated that a 15 mg dose of oxycodone HCl intranasally administered as crushed tablets or powder is liked significantly more (p ≤ 0.003) than an equivalent dose (oxycodone HCl) of crushed Acurox® Tablets. These results were supported by several secondary endpoints including a lower willingness to snort crushed Acurox® Tablets again. Snorting Acurox® Tablets induced nasal discomfort and pain in the subjects.

1.5.2.3   *Intravenous Abuse Liability*

Two laboratory studies (the Extraction Test and the Syringe Test) were conducted to evaluate abuse liability related to IV administration of oxycodone obtained from dissolved or chemically altered Acurox® Tablets. In the Extraction Test, it was determined by an independent third party laboratory that extracting oxycodone from a tablet in a form and volume suitable for IV administration was substantially more difficult and time consuming for Acurox® Tablets compared to 3 widely prescribed and currently marketed tablet products containing oxycodone. In the Syringe Test it was determined, using numerous solvents suitable for IV injection, that large volumes of solvent are required to sufficiently dissolve Acurox® Tablets to the extent that the resulting solution can theoretically be withdrawn into a needle and syringe for IV injection. The Extraction Test and the Syringe Test provide substantial evidence suggesting that Acurox® Tablets have a reduced potential for abuse for IV injection compared to currently available oxycodone-containing tablet products.

1.6   Review of Clinical Safety

The safety of orally administered Acurox® Tablets at recommended doses was evaluated in 565 subjects. No deaths or serious AEs were reported. Acurox® Tablets was safe and generally well tolerated at doses ranging from 5/30 mg q6h to 15/60 mg q6h. The treatment-emergent adverse events (TEAEs) observed in all clinical trials were similar to those observed with opioids and niacin. The AEs associated with niacin (primarily flushing and pruritus) increased with dose as part of the product design, to discourage taking doses higher than prescribed. The incidence of flushing in postoperative patients taking Acurox® Tablets for pain relief at the recommended doses ranged from 11% to 16% (compared to 1.5% for placebo). The flushing was predominantly mild and did not cause patients to withdraw from the trial.

1.7   Benefit/Risk Assessment

The FDA has stated that medicines that incrementally address the misuse, abuse, and diversion of currently available opioid drugs would be expected to have public health benefits. Acurox® is a combination drug product containing oxycodone HCl and niacin with functional excipients designed to minimize the potential for abuse.

The Acurox® Tablets development program, in conjunction with the scientific literature has established:

- Acurox® Tablets are effective in pain patients supporting the proposed indication for relief of moderate to severe pain;
- Acurox® Tablets are well tolerated when taken at recommended doses for analgesia;

- The disliking effects manifested by niacin when taken orally in excess quantities reduces the potential for abuse of oxycodone hydrochloride, the principal active ingredient in Acurox® Tablets;

- The doses of niacin that may be taken by a prospective abuser when swallowing excess doses of Acurox® Tablets are safe. This is extensively documented by studies of patients being treated chronically for dyslipidemias; and

- The potential benefits versus risks for the inclusion of niacin in Acurox® Tablets to limit or impede abuse are sufficient to warrant approval of Acurox® Tablets.

These conclusions are supported by statistically significant and clinically meaningful results from both analgesic efficacy and abuse liability studies. Acurox® Tablets provide an incremental benefit over existing IR oxycodone containing products by having the potential to reduce abuse by the 3 most common routes of administration among opioid tablet abusers: excess oral intake, nasal snorting, and IV use.

The incremental improvement in the potential to deter abuse when compared to available IR opioids is likely to be associated with a public health benefit once Acurox® Tablets are approved and used in routine clinical practice.

2. BACKGROUND AND RATIONALE

2.1 Prescribed Medical Use of Opioid Analgesics

Of the more than 75 million Americans who suffer from pain, approximately 40 million have chronic pain caused by arthritis, lower back or muscle pain, fibromyalgia, or bone/joint pain.[1] Each year, approximately 25 million Americans suffer from acute pain due to injuries or surgery.[2] It is estimated that 50 million Americans are partially or totally disabled because of pain.[3]

Opioid analgesics are safe and effective for moderate to severe pain when taken as prescribed under medical supervision.[4] Opioid analgesics are an important component in the Joint Commission on Accreditation of Healthcare Organizations' guidelines for treating moderate-to-severe pain.[3]

Given the prevalence of pain in the United States, opioid analgesics have become among the most widely prescribed category of medicines, with 254 million prescriptions for tablets and capsule products dispensed in 2009,[5] a 2% increase over the previous year. However, the demographics and prevalence of Americans in pain is unlikely to change in the near future and the use of potent and effective analgesics including opioids will remain unabated.

2.2 Misuse and Abuse of Opioids

Combining the widespread prescribing and availability of opioids with their psychoactive properties has led to the public health crisis of medical misuse and non-medical abuse. This is a complex societal problem involving both patients and non-patients and is now described as having reached epidemic proportions.[6] The statistics are staggering. According to US government surveys and projections, 34.9 million people, or more than 10% of the US population, have used prescription opioid analgesics non-medically at some point in their lifetime.[7] In the past year, the abuse of prescription opioid analgesics was second only to the use of marijuana among illicit drug users[7] and prescription opioids have now surpassed marijuana in first time illicit use. Nearly 12 million persons (4.8%) 12 years of age or older indicate non-medical use of prescription pain relievers in the past year.[7] There are approximately 250,000 emergency room visits per year related to non-medical use of prescription opioids.[8] Fatal overdoses of prescription opioids now number over 13,000 per year in US. Opioid analgesics were involved in almost 40% of all poisoning deaths in 2006, up from about 20% in 1999.[9] Over 1.6 million Americans currently meet the criteria for addiction to prescription opioids,[7] and over 85,000 admissions are reported to substance-abuse treatment facilities per year for prescription opioid abuse.[8] It is estimated that the societal costs of prescription opioid abuse total $50 billion annually.[10]

Tragically, opioid abuse in the United States can begin at an early age with 14% of the past year's opioid abusers being younger than 17 years of age.[7] A 2008 survey conducted in over 46,000 8th, 10th, and 12th grade students demonstrated that 1 in 10 twelfth-graders reported recreational use of IR hydrocodone bitartrate (contained in Vicodin® and other brands) and 1 in 20 abused OxyContin®(oxycodone HCl) ER Tablets. Alarmingly, 2.9% and 2.1% of 8th graders had used Vicodin® and OxyContin®, respectively.[11] It has been shown that some non-medical use of opioids starts earlier than age 12, and that early abuse correlates with more detrimental outcomes.[12]

The majority of abuse is associated with IR opioid analgesic products. According to the Researched Abuse, Diversion, and Addiction-related Surveillance (RADARS®) System, IR opioid products are responsible for a higher proportion of misuse, abuse, and diversion than ER opioid products.[13] In addition, studies and surveys suggest that first time abusers often start by misusing IR opioids orally. A recent Survey of Key Informants' Patients (SKIP) showed that 51% of respondents receiving treatment for opioid abuse identified IR hydrocodone initially to get "high."[14]

Over time, abusers may quickly advance to intranasal and intravenous routes of administration.[15]

An IR opioid product that introduces limits or impediments to abuse for oral, nasal, and intravenous routes of administration could be particularly beneficial.

2.2.1   Non-medical Use of Immediate-Release Opioid Products

In 2009, of the 254 million opioid analgesic prescriptions for tablets and capsules, 238 million or approximately 94% were for IR opioids. This nearly a 15-fold greater dispensing of prescriptions for IR products is likely a major factor accounting for the greater number of people abusing IR opioid products versus ER opioid products.

Of those Americans estimated to have used oxycodone-containing products non-medically in their lifetime, 4.8 million abused ER oxycodone tablets while 12.3 million abused IR oxycodone containing tablets and capsules.[7]

The abuse of IR and ER opioids are not mutually exclusive with many abusers misusing or abusing both products. For example, of the estimated 4.8 million people who abused ER oxycodone Tablets, 69% also abused IR opioids containing oxycodone.[7]

Emergency department (ED) visitation may indicate the inherent risks of IR and ER opioid products to patients and abusers. In 2006, ED visits related to IR oxycodone (and combination) products were 39,068 compared to 25,820 for ER oxycodone tablets.[8]

Much attention has been focused on ER opioid products whose ER mechanism may be readily defeated by simply chewing or crushing the products which converts them into a high dose, highly euphorigenic IR form associated with potentially substantial harmful effects. However, the need to curtail abuse, misuse, and diversion of IR opioids is equally important given: (1) the greater number of prescriptions dispensed for IR opioids compared to ER opioids making them readily available, (2) the immediate euphoria experienced by abusers of IR opioids without the need for tampering, (3) the number of harmful outcomes including deaths is greater with IR than ER opioid products (Table 1).[14]

Table 1. **RADARS System Poison Center Program Data: Intentional Exposures by Associated Medical Outcome (4Q2008 – 3Q2009)**

	Immediate Release Opioids n (%)	Extended Release Opioids n (%)
Total, n	24,243	5,247
Associated Medical Outcome, n (%)		
Major Effect	1,255 (5.18)	646 (12.31)
Death – Direct Report	115 (0.47)	51 (0.97)
Death – Indirect Report	3 (0.01)	4 (0.08)

2.2.2   *Types of Non-medical Use of Opioids*

It is useful to characterize the populations at the center of the prescription opioid crisis. In addition the patients that misuse their legitimate prescription, usually by over-consumption, they can be divided into 3 broad categories as shown in Table 2, recognizing that these populations are varied and the characteristics greatly overlap.

Table 2. **Characteristics of Abuse Populations**

Abuser Populations	Characteristics and Goals for Reducing Abuse
Novice, experimenter	• Likely to be experimenting with different opioids and doses but not necessarily pushing the dose to extremes to achieve the "best high" • Swallowing excess numbers of whole IR tablets is the most common abuse method • Less likely to abuse nasally • Not likely to extract for IV administration • Goal: Reductions in overdose, death and progression to addiction are a high priority
Established, non-dependent	• Oral and nasal routes are most common • Availability is of significant importance • Goal: Reduction in addiction, overdose, and death are a high priority
Dependent addict	• Physical and chemical manipulation, extractability and availability of alternatives are important • Population is considerably smaller • Will go to greater lengths to avoid withdrawal

The greater use of IR opioids among new initiates to abuse is not surprising given the large number of dispensed prescriptions, and thus availability of IR opioids. In fact, 56% of abusers indicate they receive their drugs from friends and family.[7] As new abusers experiment, their experience with higher oral doses and different opioids becomes greater.

Figure 1 describes the number of days opioids were abused in the last 12 months by people who have abused IR oxycodone at some point in their lifetime. IR opioids are likely abused by new initiates, as well as experimenters, recreational drug users, and habitual/addicted drug abusers.

Figure 1.   Frequency of Abuse of Opioid Products During the Past Year

**Frequency of Abuse of Prescription Opioids
By People Who Have Abused IR Oxycodone**

Source: 2008 NSDUH, Percocet, Percodan and Tylox Lifetime
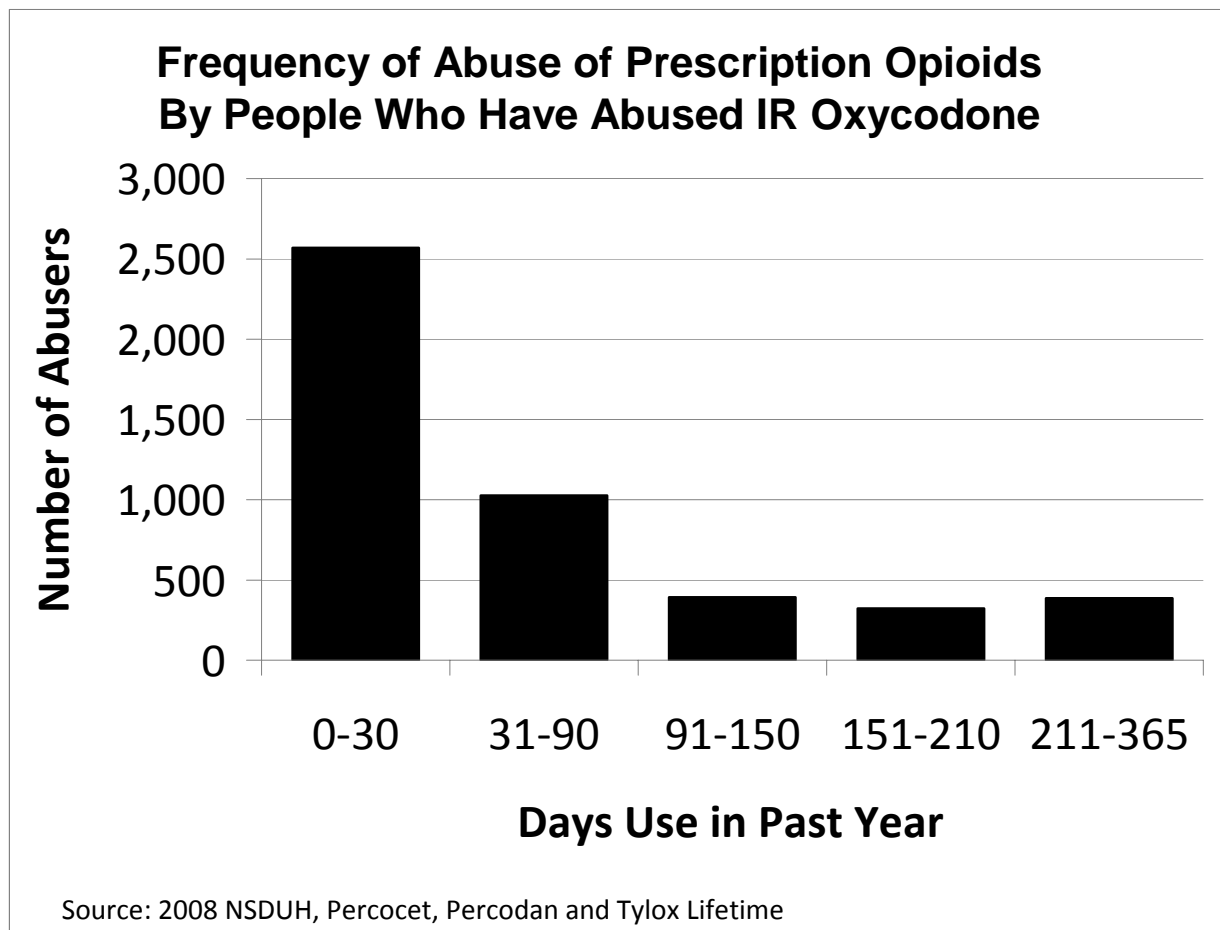
2.2.3   *Routes of Opioid Abuse and Misuse*

The routes of opioid abuse vary by product. Table 3 summarizes routes of administration for non-medical use of oxycodone and hydrocodone in several series of studies from 2006 to 2008.

Oral ingestion of prescription opioids is the most prevalent route of abuse and is the route preferred by novices and new initiators of opioid abuse.[15,16,17] In a recent survey of college students who identified themselves as non-medical users of IR opioids and with low Drug Abuse Screening Test scores suggesting early abuse, 88% stated that they abused by the oral route, 7% abused nasally, and 3.6% abused by injection.[14]

As noted in Table 3 for the oxycodone studies, the prevalence of oral opioid abuse is higher in general abuse population studies as compared to substance-abuse centers supporting the assumption that more advanced abusers migrate to more potentially hazardous routes of administration. The data also suggest that oral abuse is more prevalent with IR opioid products compared with ER products. Participants in the Opioid Treatment Program and the SKIP Program commonly abuse opioids by the oral route; however, 32% and 23% of these respondents, respectively, also have abused opioids by the intravenous route.[14]

The particular route of administration is associated with differential detrimental health consequences. In the RADARS® System Opioid and Stimulant Poison Center (PC) (i.e., RADARS-PC) database, the percentage of prescription opioid exposures leading to a major effect or death was 8.6% of oral ingestions, 10.2% of inhalations, and 16.5% of injections.[7] Injection of prescription opioids has also been associated with dramatically higher rates of human immunodeficiency virus (HIV) infections, hepatitis, cellulitis, foreign matter emboli, and other complications of needle use.[18] There is evidence that abuse among novices tends to be oral, while snorting and IV abuse occurs with more experienced abusers.[16] This suggests that some abusers progress to increasingly more hazardous methods of abuse although there is clear danger with any type of abuse.

Table 3.   **Routes of Administration for Selected Prescription Opioids Used Non-Medically: Summary of Studies**

Opioid Product[a]	Product Type/Brand Name	Reference[b]	Study Population	Ingestion[c]	Inhalation[d]	Injection[e]
Oxycodone	All IR and ER products	(Butler et al, 2008)[19]	Substance-abuse treatment	77%	45%	22%
	All IR and ER products	(Rosenblum et al, 2007)[20]	Substance-abuse treatment	—	—	35%
	OxyContin® (ER)	(Katz et al, 2008)[21]	General population of abusers	89%	85%	26%
		(Passik et al, 2006)[22]	Substance-abuse treatment in Kentucky	49%	92%	23%
		(Butler et al., 2006)[23]	Substance-abuse treatment	27%	57%	59%
	Percocet® (IR with acetaminophen)	(Butler et al., 2006)[23]	Substance-abuse treatment	83%	44%	0.5%
Hydrocodone	All IR products	(Butler et al, 2008)[19]	Substance-abuse treatment	87%	24%	1%
	Any formulation	(Rosenblum et al, 2007)[20]	Substance-abuse treatment	—	—	8%
	Vicodin® (IR with acetaminophen)	(Katz et al, 2008)[21]	General population of abusers	91%	18%	0%
	Lortab® (IR with acetaminophen)	(Butler et al., 2006)[23]	Substance-abuse treatment	89%	40%	1%

[a] Includes combination products, when data are available.

[b] All percentages from Butler et al (2008) are approximations derived from visual interpretation of Figure 7 of this source.

[c] Includes swallowing and chewing.

[d] Includes snorting and smoking (when data are available).

[e] Includes all parenteral routes.

NOTE: Abusers may use more than 1 route of abuse; therefore, some rows may add to >100%.

2.3 Regulatory Responses to Opioid Abuse and Misuse

A public health dilemma has arisen in the US as a consequence of the need to use opioids to achieve more effective analgesia and the resultant opioid misuse and abuse Maximizing the benefits of opioids, while mitigating risk, is an unambiguous public health priority.

The FDA recognizes the difficulty of balancing the availability of effective pain management products with drug safety concerns. This was described by Dr. Janet Woodcock of the FDA in a recent perspective published in the New England Journal of Medicine.[24] One approach encouraged by FDA, CDC, and other government agencies is to formulate opioid products with properties intended to introduce limits or impediments to abuse.

The FDA has stated that medicines that incrementally decrease the abuse of currently available opioid drugs would be expected to have public health benefits. This was also the opinion of a recent FDA Advisory Committee discussing this issue.[25] The FDA also recognizes that only epidemiology studies carried out over an extended period of time can accurately assess if a product reduces non-medical use in the community relative to that of comparable products.[26] However, demonstrating that a new medicine reduces non-medical use in the community first requires for it to be approved for use in patients and this in part depends on being able to demonstrate prior to approval that the new medicine has the potential for less abuse than that of suitable comparators. This is typically done through a battery of in vitro and in vivo abuse liability studies while the product is in development. Outcome measures used in human abuse liability studies, such as Disliking/Liking scores and Take Drug Again assessments, are used as surrogate measures for behaviors of abusers in the community. It is not known how these measures will translate into a decrease in the rate of abuse and misuse in the community. Hence data from abuse liability studies are not appropriate for supporting a labeling claim for an indication of abuse deterrence. Obtaining such an explicit indication will require demonstration of comparative reduced abuse rates using longitudinal epidemiological data. However, as stated above, even an incremental decrease in the abuse potential of an abuse deterrent formulation is likely to result in a public health benefit.[25]

In summary, and as described in Section 3, the objective of the Acurox® Tablets development program was to develop a product that safely and effectively relieves moderate-to-severe pain and simultaneously provides an incremental reduction in abuse liability potential compared to currently marketed IR oxycodone HCl tablets.

2.4 Rationale for Developing Acurox® Tablets

Applying innovative technologies to provide limits and impediments to the misuse and abuse of IR opioids may translate into important individual and societal benefits. Specifically the technology should seek to limit the behaviors of misuse and abuse in a cross section of the population at risk by decreasing the risks of overdose, repetitive use and addiction.

As previously outlined, IR opioids are the starting point for abuse, and play a critical role in the "abuse trajectory" of ever increasing riskier behaviors of opioid abusers. IR opioids from legitimate prescribing channels are the most readily available opioids for unsophisticated new drug abusers to access for experimentation. Data show that abusers of IR opioids often obtain them from parents and acquaintances.[27] Data also indicate that early use of prescription

opioids is a predictor of later abuse and dependence.[12] As an abuser's experience increases and they adapt to new and potentially more hazardous drug delivery methods, studies indicate IR opioids continue to play a substantial role in this progression being used intranasally and intravenously and by habitual/addicted abusers daily. Abusers are using both IR and ER opioids interchangeably.[14]

Education, intervention, and treatment programs have taken us only so far. Acurox® Tablets have been developed to be an effective and well tolerated IR opioid analgesic that has the ability to reduce the potential for abuse. The goal was to introduce limits and impediments to abuse as opposed to the outright elimination of abuse. Specifically, the development has focused on the 3 most common methods of abuse for IR opioids, namely oral misuse and abuse by over-consumption as well as nasal and IV abuse. A key development objective was to demonstrate that Acurox® represents an incremental improvement over existing IR opioids.

Novice, Experimenter

The data indicate that initiation of non-medical use of opioids is often associated with younger people, usually teenagers, and that the first experience is likely to be with an opioid obtained from a friend or family member.[14,27] The data further supports that these new initiates typically start abuse via the oral route. But, we recognize many abusers progress to more potentially hazardous doses and routes of administration. Therefore this naïve population often experiments with dose and route of administration to attain the desired effect.

Established, Non-dependent

Almost half of opioid abusers are taking opioids for more than 30 days per year.[7] These habitual abusers may be non-dependent and likely have a preferred dose and route of administration. Nasal and even IV administration are likely more prevalent in this user group since these methods are perceived to attain a more pronounced effect and faster onset than the oral route.

Dependent Addict

Physically and psychologically dependent abusers are a significant challenge as they require continued administration of opioids to prevent withdrawal and introduction of an opioid antagonist may have a harmful impact. In this group, nasal and, more likely, IV administration is more typical than with novice users and established, non-dependent users.

3.   ACUROX® TABLETS

3.1   Aversion® Technology

Acura Pharmaceuticals, Inc. (Acura) developed the Aversion® Technology used in Acurox® Tablets to introduce limits or impediments to abuse as opposed to the outright elimination of abuse. Drug products developed utilizing Aversion® Technology are intended to limit or impede oral swallowing of excess numbers of tablets, nasal snorting of crushed tablets, and intravenous injection of dissolved tablets.

3.2   Acurox® Tablets Formulation Development

Acurox® Tablets are an IR combination product containing 2 active ingredients and an essential composition of functional inactive excipients. Each Acurox® Tablet contains oxycodone HCl as the principal active analgesic ingredient. Niacin, the second active ingredient included in each tablet, is intended to minimize the potential for oral and nasal abuse of the principal active ingredient by inducing drug disliking effects at potentially abused doses (Clinical studies of the oral abuse liability potential of Acurox® are presented in Section 6.2). The choice of niacin as the second active ingredient in Acurox® Tablets is described in Section 5. The excipients in Acurox® Tablets are listed in the FDA's Inactive Ingredient Guide (IIG) and/or are Generally Recognized as Safe substances. These essential functional excipients quickly form a viscous gel when the tablets are dissolved in various solvents for IV injection. The formation of this viscous gel substantially impedes the ability to extract oxycodone from the tablets or to draw the resulting material into a syringe. (Laboratory tests demonstrating these properties are presented in Section 6.2.3.) In addition, if Acurox® Tablets are crushed and snorted, the essential composition of functional excipients and potentially the niacin contained in Acurox® Tablets significantly reduce "drug liking" compared to other oxycodone products administered intranasally. (Studies demonstrating the nasal abuse liability potential of Acurox® Tablets are presented in detail in Section 6.2.2).

In summary, the unique composition of active and inactive ingredients in Acurox® Tablets was designed to effectively relieve moderate-to-severe pain while simultaneously introducing limits or impediments to abuse for the 3 most common methods of IR opioid tablet abuse, including:

1. Intentional swallowing of a quantity of tablets exceeding the proposed usual recommended dose;

2. Nasal administration of crushed tablets; and

3. Physical and/or chemical manipulation of tablets into a solvent suitable for IV injection using a needle and syringe.

3.3   Populations Intended to Benefit from Acurox® Tablets

Acurox® Tablets are intended for any patient with moderate to severe pain where the use of an immediate release opioid analgesic tablet is appropriate. It is important to understand that Acurox® Tablets should not be prescribed for patients anticipated to require dose escalation

above the proposed recommended dose due to the possibility of inducing undesirable niacin effects.

For patients who intentionally over-medicate with Acurox® by swallowing more tablets than prescribed by their physician and for the non-patient abusing Acurox® by a variety of methods, the benefit is in decreasing behaviors associated with harmful and potentially lethal outcomes. This is primarily at the level of the individual, but carries substantial societal implications. The benefit is anticipated to result from the niacin induced disliking effects in conjunction with the functional inactive ingredients in Acurox® as demonstrated in the abuse liability program (AP-ADF-102, AP-ADF-106, AP-ADF-111 AP-ADF-114, Syringe Test, and Extraction Test). The benefits of Acurox® to society, an individual who attempts to misuses the product, or an abuser may depend on the experience of the individual concerned (see Table 4).

Those individuals in the early stages of experimenting with opioids, often young people, may not initially benefit from Acurox®. Typically, this group might take 1-3 tablets orally and niacin is unlikely to be aversive at these low doses. However, the aversive effect of niacin in Acurox® at higher than these doses has the potential to discourage this population from progressing to oxycodone oral doses associated with harmful and potentially lethal effects. In addition, Acurox® could limit progression to other routes of abuse such as snorting where even at relatively low doses of oxycodone, Acurox® Tablets have demonstrated a reduction in the potential for abuse (Study AP-ADF-106).

In the established non-dependent opioid abusers, the oral and nasal routes of administration are more common. Likability of the opioid is a priority to this group and reinforcement increases the oxycodone dose requirements. The aversive effects of niacin in Acurox® Tablets at these higher and potentially harmful oxycodone doses may help to prevent overdose and death in some people. The aversive effects of Acurox® Tablets associated with snorting and the impediments to IV injection could limit progression to these more dangerous behaviors.

In addicts, physical and chemical manipulation, extractability, and likeability are key considerations. Acurox® was developed to limit or impede oral, intranasal, and intravenous routes of abuse so prevalent in this population. The impediments to abuse designed into each Acurox® Tablet may cause addicts to seek more desirable opioid alternatives.

Niacin deters oral abuse by inducing disliking, and precipitates the signs and symptoms of flushing in individuals who take excess oral doses of Acurox®. Whereas at excess oral doses individuals may be at risk of the well recognized harmful effects of high doses of oxycodone, there is no evidence that niacin doses contained in Acurox® Tablets at these excess oxycodone doses is anything other than an annoying, clinically benign cutaneous phenomenon associated with self-resolving disliking effects. Niacin therefore contributes to a minimal incremental risk. The safety record of niacin contained in single excess quantities of Acurox® is supported by decades of clinical experience in patients being treated chronically for dyslipidemias at niacin doses greater than 1000 mg per day.

3.4   Potential Risks Associated with Acurox® Tablets

Both pain patients and potential abusers are subject to the risks associated with opioids that are well known from decades of experience in clinical practice and drug abuse settings. In

this regard, exposure to Acurox® Tablets carry the same risks as exposure to other IR oxycodone containing products.

Patients taking Acurox® Tablets will also be exposed to niacin. Clinical experience suggests that approximately 10 to 15% of pain patients may experience an increased incidence of mild to moderate flushing associated with niacin. Abusers taking excess oral doses of Acurox® Tablets will be exposed to higher levels of niacin and thereby be subject to the disliking effects induced by higher doses of niacin. The safety of niacin is discussed in more detail in Section 5.

Table 4.   Characteristics of the Misuse and Abuse of Prescription Opioids –Potential Benefit from the Abuse Deterrence Properties of Acurox®

Effect Sought by Abuser	Medical/Non-medical Abuse/Misuse	Demographic[1]	Route of Administration	Risk/Harm	Potential Benefit from Acurox®
Experimentation with psychoactive products	Non-medical abuse of diverted opioid	A	Primarily oral	Overdose and death Reinforcement leading to repetitive use and higher doses	Deters use due to dislike of niacin effect if taken in excess doses
Euphoria associated with rapid rise of high opioid dose	Non-medical abuse of diverted opioid	A and B	Primarily oral. Can lead to inhalation or intravenous use	Overdose and death Inhalation and IV use associated with addiction and co-morbidities	Deters use due to dislike of niacin effect if taken in excess doses. Limits and impediments to snorting and injecting
Pain relief in non-medical setting	Non-medical abuse Self-treatment with diverted opioid	All age groups	Primarily oral	Overdose and death Reinforcement leading to repetitive use	Deters use due to dislike of niacin effect if taken in excess doses
Pain relief when patient is not satisfied with relief provided by physician's prescribed dose	Misuse of prescribed opioid	General population	Oral excess	Overdose and death Reinforcement leading to repetitive use	Deters use due to dislike of niacin effect if taken in excess doses
Emotional support for stress, anxiety, depression	Misuse of prescribed opioid Abuse of diverted opioid	General population	Oral primarily	Overdose and death Reinforcement leading to repetitive use	Deters use due to dislike of niacin effect if taken in excess doses
Dependence, addiction	Abuse of diverted opioid	C	Inhalation, intravenous predominate	Overdose and death, co-morbidities	Limits and impediments to snorting and injecting may occur but hard-core addicts may find a way to abuse
Suicide attempt	Abuse	A	Oral excess primarily	Overdose and death	Unlikely to impact determined attempt

[1] A = Novice, Experimenter; B = Established, Non-dependent; C = Dependent Addict

3.5   Proposed Indication, Dosage Strengths and Dosing Regimen

The proposed indication for Acurox® Tablets is the relief of moderate-to-severe pain where the use of an IR, orally administered, opioid analgesic tablet is appropriate. Acurox® Tablets should not be prescribed for patients requiring dose escalation above the recommended dose due to the possibility of inducing undesirable niacin effects.

Acurox® Tablets will be available as:

- 2 x Acurox® Tablets 5/30 mg or 2 x Acurox® Tablets 7.5/30 mg every 6 hours (q6h) as needed depending on initial pain intensity.
- If deemed necessary to initiate therapy at a lower dose, patients may be started on 1 x Acurox® Tablet 5/30 mg or 1 x Acurox® Tablet 7.5/30 mg q6h as needed.

3.6   Pharmacology

3.6.1   Oxycodone

Oxycodone is a pure opioid agonist whose principal therapeutic action is analgesia. In addition to analgesia, other pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression. Like all pure opioid agonist analgesics, there is increasing analgesia with increasing doses and no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression. This is in contrast to mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses.

Oxycodone produces respiratory depression, likely by a direct action on brain stem respiratory centers. Oxycodone causes miosis, even in total darkness. Oxycodone, in therapeutic doses, produces peripheral vasodilation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, orthostatic hypotension and cardiovascular collapse.[28]

3.6.2   Niacin

Niacin (vitamin B_3) is the common name for nicotinic acid. As a B vitamin, niacin is essential for the normal function of the nervous system and the gastrointestinal tract. The pharmacology of niacin is presented in Section 5.2.

3.7   Pharmacokinetics

The pharmacokinetics of oxycodone are well described.[28] The *in vivo* performance (i.e., bioavailability) of oxycodone in Acurox® Tablets was evaluated in three Phase 1 studies: (a) to determine the bioavailability of Acurox® Tablets relative to the FDA's designated Reference Listed Drug (RLD) for IR oxycodone HCL tablets (AP-ADF-104), (b) to assess the dose proportionality and effects of food on Acurox® Tablets (AP-ADF-108), and (c) to determine the steady-state pharmacokinetics of Acurox® Tablets (AP-ADF-109). In addition,

the pharmacokinetics of Acurox® Tablets when administered by an unintended route (i.e., intranasally) were evaluated in the context of an abuse liability study (AP-ADF-106).

Study AP-ADF-104 demonstrated the bioequivalence of Acurox® Tablets to the RLD, Roxicodone® (oxycodone HCl tablets, USP), in an open-label, randomized, two-period, crossover study in 40 healthy volunteers. Acurox® (oxycodone HCl/niacin) was administered as three 5/30 mg tablets (total dose of 15/90 mg) and the RLD was administered as a single 15 mg tablet. The pharmacokinetic results indicated that the 90% confidence intervals for peak exposure based on $ln(C_{max})$, $ln(AUC_{last})$ and $ln(AUC_{inf})$ of oxycodone were within the 80% to 125% range indicating that three Acurox® Tablets are bioequivalent for oxycodone to a single tablet of the RLD, Roxicodone® 15 mg tablets, under fasting conditions.

Study AP-ADF-108 evaluated the pharmacokinetics and dose proportionality of oxycodone after a single-dose administration of 1, 2, and 3 Acurox® Tablets 5/30 mg, and the effects of food on oxycodone bioavailability after single-dose administration of Acurox® Tablets under fed conditions (standard high-fat breakfast) compared with fasted conditions. Based on linear regression analysis of the dose-normalized values of C_{max}, AUC_{last}, and AUC_{inf}, the 3 dose levels of Acurox® Tablets were dose proportional under fasting conditions. The conclusions from this study were that there was no significant food effect with respect to oxycodone C_{max} but a significant food effect ($p < 0.05$) with respect to the total systemic exposure (AUC) from Acurox® 5mg/30mg tablets. This is consistent with the known interaction of food on absorption of oxycodone.

Study AP-ADF-109 was a multiple-dose study to assess the single- and multiple-dose pharmacokinetics and dose proportionality of Acurox® Tablets following administration of 1 versus 2 tablets every six hours for three-and-a-half days in a 2-way cross-over study. Steady state conditions for oxycodone were achieved on Day 2 with both doses. The dose adjusted 90% confidence interval for the ratio of maximum exposure, based on $ln(C_{max})$, was not within the accepted 80% to 125% limits for bioequivalence on Day 1 but was within the bioequivalence limits on Day 4.5. Confidence intervals for total systemic exposure, based on $ln(AUC_{last})$ and $ln(AUC_{inf})$, were within the accepted bioequivalence limits on both Day 1 and Day 4.5.

Study AP-ADF-106, an abuse liability study, evaluated the pharmacokinetic (PK) characteristics of Acurox® Tablets when administered by an unintended route (i.e., tablets crushed and administered intranasally) in 17 recreational opioid users. (See Section 6.2.2.1 for the abuse liability components of this study.) The pharmacokinetics of crushed Acurox® Tablets (2 × 7.5/30 mg), crushed Roxicodone® (oxycodone HCl) Tablets (1 × 15 mg), and oxycodone HCl powder, 15 mg, all administered intranasally, were compared. There were no statistically significant or clinically meaningful differences between the 3 treatments in terms of maximum plasma concentration or total systemic exposure, indicating that oxycodone bioavailability was similar between the 3 dosage forms. Safety results from this study are summarized in Section 5.6.2.2.

4.   REGULATORY HISTORY

The initial Investigational New Drug (IND) Application for Acurox® Tablets was submitted to the FDA on March 7, 2005. At the February 10, 2006 End-of-Phase-2 meeting, the Agency agreed that a single adequate and well-controlled study (Study AP-ADF-105) would be sufficient to provide substantial evidence of the safety and efficacy of Acurox® Tablets for the proposed indication for relief of moderate-to-severe pain. The New Drug Application (NDA) was submitted in December 2008, accepted for filing in February 2009, and assigned a priority review classification.

On June 30, 2009, the Agency issued a Complete Response Letter questioning the relative contribution of niacin to minimize the potential for oral abuse of oxycodone HCl, the principal active ingredient in the product. The FDA further noted the observed incidence of flushing in some patients receiving proposed recommended doses of Acurox® Tablets appeared to be greater than oxycodone HCl alone leading the FDA to question the benefit/risk of the niacin ingredient in Acurox®. The relevant combination drug regulation (21 CFR paragraph 300.50) states:

"Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Special cases of this general rule are where a component is added:

1. *To enhance the safety or effectiveness of the principal active component; and*

2. *To minimize the potential for abuse of the principal active component"*

On September 2, 2009, the FDA's Division of Anesthesia, Analgesia and Rheumatology Products, Acura Pharmaceuticals, Inc., and King Pharmaceuticals, Inc. met to discuss the Complete Response Letter. As a result of the meeting, the FDA concluded that an Advisory Committee would be convened to evaluate the evidence for combining niacin with oxycodone HCl in Acurox® Tablets, and advise the FDA on the overall benefits to risk balance of the product.

5. NIACIN IN ACUROX® TABLETS

5.1 Niacin Background

In its review of the Acurox® Tablets NDA, the FDA identified the occurrence of mild to moderate flushing, ascribed to niacin and reported by some patients in clinical trials, following exposure to the proposed recommended doses of Acurox® Tablets. This was the FDA's only safety issue expressed in the Complete Response Letter. In the Complete Response Letter the Agency also noted the potential impact of food and NSAIDs on mitigating the disliking effects of niacin when Acurox® is taken in excess oral doses.

The purpose of this section is to: (1) explain the rationale for the inclusion of niacin in Acurox® Tablets; (2) demonstrate that it is safe to administer niacin at the proposed recommended doses in Acurox® Tablets; (3) describe how the dose of niacin in each Acurox® Tablet was selected; (4) provide information about potential mitigation of niacin disliking effects by food or NSAIDs; and (5) show that there is compelling evidence that Acurox® Tablets have an acceptable safety profile compared to oxycodone HCl without niacin.

5.2 Niacin Pharmacology: Flushing and the Role of Prostaglandins

Niacin (vitamin B_3) is the common name for nicotinic acid. It is an essential nutrient, and the Recommended Dietary Allowance is 16 mg/day for men and 14 mg/day for women[29]. Nicotinic acid is present in the body as its active form, nicotinamide. Nicotinamide functions in the body as a component of 2 coenzymes that support oxidation-reduction reactions: nicotinamide adenine dinucleotide, coenzyme I and nicotinamide adenine dinucleotide phosphate, coenzyme II. As a B vitamin, niacin is essential to support energy metabolism and for the normal function of a variety of tissues including the nervous system and the gastrointestinal tract.[30]

Following an oral dose, nicotinic acid is rapidly absorbed with peak concentrations occurring within 1 hour after dosing. Approximately 88% of an oral dose is eliminated by the kidneys as unchanged drug and nicotinuric acid, its primary metabolite. The elimination half-life of niacin is 20-45 minutes.[31]

The vasocutaneous flushing reaction of niacin occurs in Langerhans cells of the skin by activation of the GPR109A (niacin) receptor and production of prostanoids including prostaglandin D2 (PGD2) and prostaglandin E2 (PGE2). These in turn activate the DP-1, EP-2, and EP-4 receptors resulting in vasodilation and flushing. Niacin increases plasma levels of PGD2 within 12 to 45 minutes. Potential approaches to reduce or prevent niacin-induced flushing include decreasing prostanoid synthesis in the skin using aspirin and other NSAIDS.[32]

Tolerance to niacin-induced flushing develops after one or more weeks of continuous dosing. This is a result of decreased prostaglandin production with repeated doses. The flushing response is restored if niacin is stopped for several days, and then re-instituted. Furthermore, if the dose of niacin is increased, the flushing response returns.[33]

These characteristics of tolerance to niacin flushing are important when considering the abuse-deterrent effects of niacin in Acurox® Tablets. As noted in Figure 1, the majority of

people who abuse opioids do so sporadically (≤30 days a year). Hence, the development of tolerance to the disliking effects of niacin in a majority of abusers who swallow more than the proposed recommended analgesic doses of Acurox® Tablets is unlikely.

5.3   Rationale for the Use of Niacin in Acurox® Tablets

The development of products to decrease the oral abuse and misuse of IR opioids presents different challenges than that for ER opioid products. The attraction of an ER opioid tablet or capsule for non-medical use is that a large dose of opioid may be contained within the extended release matrix. This entire dose can be released by tampering, such as chewing, essentially converting the tablet into an IR formulation. This large dose of immediate release opioid is euphorigenic. Achieving a similar euphorigenic effect with an IR opioid requires the consumption of multiple tablets or capsules in excess of proposed recommended doses to achieve sufficient opioid exposure. To deter oral abuse of an IR opioid, the product must discourage use when the dosage form is swallowed intact or even after chewing. Furthermore, the agent must be safe and generally well tolerated at recommended doses for analgesia, but elicit safe, but otherwise disliked effects when taken at higher than recommended doses.

The rationale for selecting niacin for inclusion in Acurox® Tablets is as follows: (1) niacin does not cause harm. This is well documented in the literature and from extensive clinical experience for chronically administered approved IR and ER niacin products used for dyslipidemias at total daily doses up to 6,000 mg and 2,000 mg, respectively; (2) niacin is safe and generally well tolerated at proposed recommended doses of Acurox® as demonstrated in Study AP-ADF-105 (see Section 5.6.1) and; (3) niacin is a pharmacologically appropriate choice to combine with an opioid analgesic as a second active ingredient intended to minimize the potential for abuse of the opioid as demonstrated in Studies AP-ADF-102, AP-ADF-111, and AP-ADF-114 (see Section 6.2).

5.4   Selection of Niacin Dose in Acurox® Tablets

5.4.1   Niacin Dose-Ranging Studies

Three studies (AP-ADF-101, AP-ADF-103, and AP-ADF-107) were conducted to determine the optimal dose of niacin to include in each Acurox® Tablet. Study AP-ADF-101 evaluated the dose-response for niacin-induced side effects in the Acurox® Tablet formulation (without oxycodone HCl) at single niacin doses in the Acurox® Tablet matrix of 0, 15, 30, 45, 60, and 75 mg. Overall, niacin was generally well tolerated at each of the doses tested in this study. In each of the dose groups, ≥44% of subjects reported no symptoms and nearly 50% or more of subjects reported a tolerability score of "0 - no effect," up to the 75-mg dose. Niacin-related side effects were not observed at any dose in subjects who ingested niacin with a high fat meal. In the fasted subjects, the 15- mg and 30-mg doses of niacin were generally similar to placebo in the number of subjects reporting niacin effects, the total number of niacin effects reported and overall tolerability ratings of "no effect" or "easy to tolerate." In the fasted subjects, there was an increase in the number of subjects reporting niacin effects and the total number of niacin effects reported in the 45-mg, 60-mg, and 75-mg dose groups versus the 30-mg dose group. Study AP-ADF-101 data suggested that a single dose of ≤30 mg niacin is unlikely to lead to perceptible signs and symptoms associated with

niacin-induced vasodilation. This dose of niacin is similar to the amount in many commercially available over-the-counter nutritional products.

Study AP-ADF-107 evaluated the dose-response for niacin-induced flushing, and safety and tolerability of single doses of niacin (0, 30, 60, 90, 120, 240, 360, 480, and 600mg) in fasted and fed healthy, adult subjects. Niacin was administered in the Acurox® Tablet matrix. The results indicated that niacin would be well tolerated up to 60 mg per dose and would likely be well tolerated at 90 mg per dose. Most fasted subjects reported undesirable side effects when exposed to higher doses of niacin (120-600 mg). Subjects exposed to high doses of niacin after consuming a high-fat meal experienced less frequent and less severe undesirable side effects compared to fasted subjects. At niacin doses of 480 and 600 mg, ≤12% of fed subjects in each dose group reported poor tolerability ("unpleasant and difficult to tolerate" or "intolerable and would never take again"). There were no deaths or SAEs. All AEs were mild or moderate in severity. A niacin dose-response relationship was observed in the overall incidence of AEs in fasted subjects, as well as the specific AEs of flushing and pruritus. The most frequently reported AEs were those commonly associated with niacin administration: flushing (see Figure 2), pruritus, and paraesthesia. The incidence of these three AEs was higher in fasted subjects compared to fed subjects.

Figure 2.   Incidence of Flushing in Study AP-ADF-107
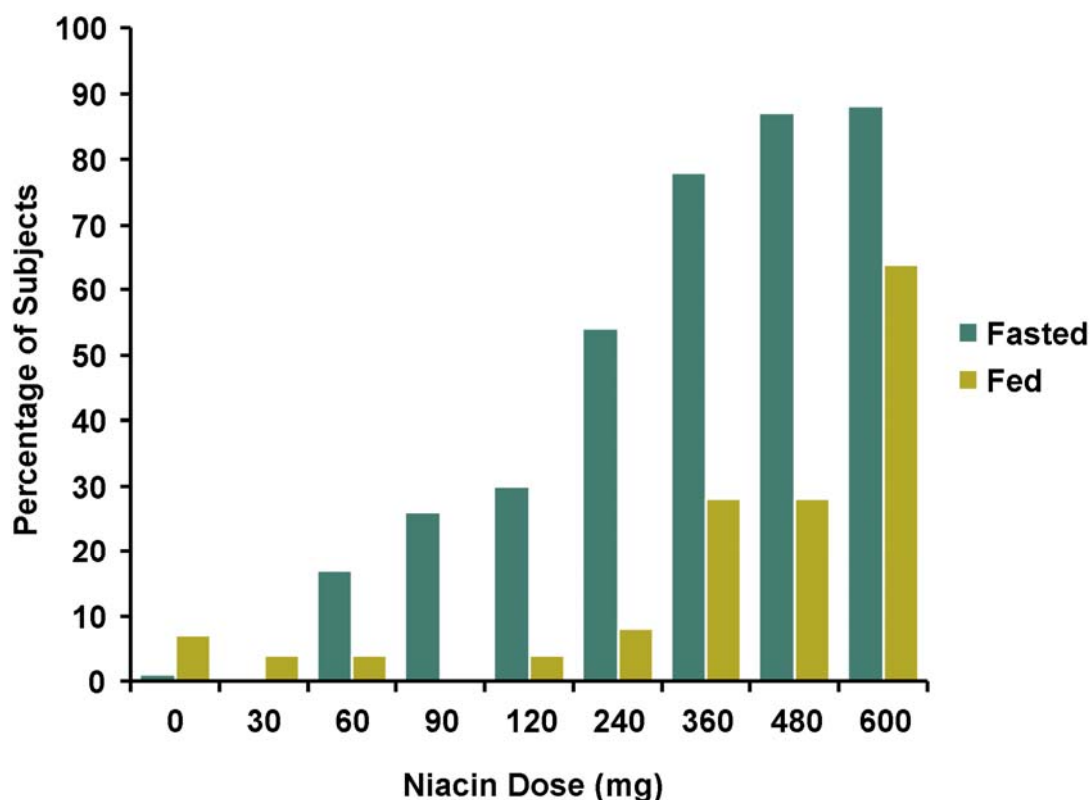
Study AP-ADF-103 evaluated the safety and tolerability of multiple doses (every 6-hour dosing for 10 days) of Acurox® Tablets with and without niacin in 66 healthy adult subjects (3 treatment groups of oxycodone HCl/niacin at 5/0 mg, 5/30 mg, and 5/60 mg; 22 subjects/group). The predominant niacin effects experienced by subjects taking 5/30 mg or 5/60 mg versus 5/0 mg were flushing, tingling, and warm feeling. Importantly, all subjects reported similar tolerability scores regardless as to whether or not they received niacin. Approximately 75% of all subjects in all groups rated the tolerability of study drugs as "easy to tolerate" or "no effect." At least one-third of subjects taking either dose of oxycodone HCl and niacin reported no niacin effects. Based on these results, it was anticipated that subjects would tolerate 2 x Acurox® Tablets (2 × 5/30 mg for a total of 10/60 mg) as a single dose administered every 6 hours.

Summary

Based on the known pharmacology of niacin and results from Studies 101, 103, and 107, it was determined that 60 mg of niacin per dose would likely be well-tolerated and 30 mg of niacin in each Acurox® Tablet for up to a 2 tablet dose would not add appreciable safety risks to pain patients. It was also hypothesized that if Acurox® Tablets were taken in excess oral doses, niacin would induce unpleasant effects that could limit or minimize the potential for abuse.

5.4.2   Safety of High Dose Niacin (≥1000 mg)

The safety of the proposed single dose and dosing interval of niacin in Acurox® Tablets (up to 60 mg every six hours) is supported by over 5 decades of clinical use of niacin at doses >1,000 mg/day to treat lipid disorders across many demographically diverse populations (age, gender, co-morbid conditions). It is important to recognize that although the total daily dose of niacin during Acurox® therapy is up to 240 mg, each single dose of up to 60 mg is essentially completely eliminated before the next dose is given due to the short niacin half-life (20 to 45 minutes). Furthermore, for patients already on a lipid lowering dose of niacin, the recommended dose range for IR niacin is up to 6000 mg daily.[31] with doses of 10,000 mg or more documented in the literature and clinical trials to treat dyslipidemias.[34] Consequently, adding an additional 240 mg of IR niacin per day to a lipid-lowering dose of niacin that is well tolerated by a particular patient is unlikely to result in safety concerns.

The clinically relevant niacin induced effects, such as elevated liver function tests, occur at doses ≥1,000 mg daily and are low in incidence (<1% of patients).[35,36]

Niacin induced skin flushing may occur with single oral doses as low as 50 mg. Based on these observations, a tolerable upper limit (Lowest Observed Adverse Effect Level) of 35 mg has been established with respect to cutaneous effects.[29] These findings are consistent with the results of studies AP-ADF-101 and AP-ADF-107.

Niacin is not significantly metabolized by cytochrome enzymes.[37] For this reason, there are no significant pharmacokinetic drug-drug interactions. Pharmacodynamic drug interactions with lipid-lowering doses of niacin (generally ≥1000 mg/day) are labeled for statins (skeletal muscle effects) and other vasoactive drugs.

Tolerance to niacin induced flushing may develop over several weeks of continuous use. However, a patient who stops taking niacin for several days will have the flushing response

restored when another dose of niacin is taken. Furthermore, if the dose of niacin is increased in a "tolerant" patient, the flushing response returns. This is demonstrated in Figure 3 by the increase in the number of flushing episodes.[33] This is an important consideration for people who both misuse or abuse opioids and who may be on other sources of niacin (e.g., to treat lipid disorders), or alternatively who may be on a stable dose of Acurox® Tablets and increase their tablet intake to levels exceeding the proposed recommended doses. As the dose of niacin is increased, the flushing response and associated disliking effects will be restored. Co-administration of niacin with food or an NSAID mitigates flushing in some, but not all people (see Section 5.5).

Figure 3.   Incidence of Flushing Over Time and With Dose Escalation[33]
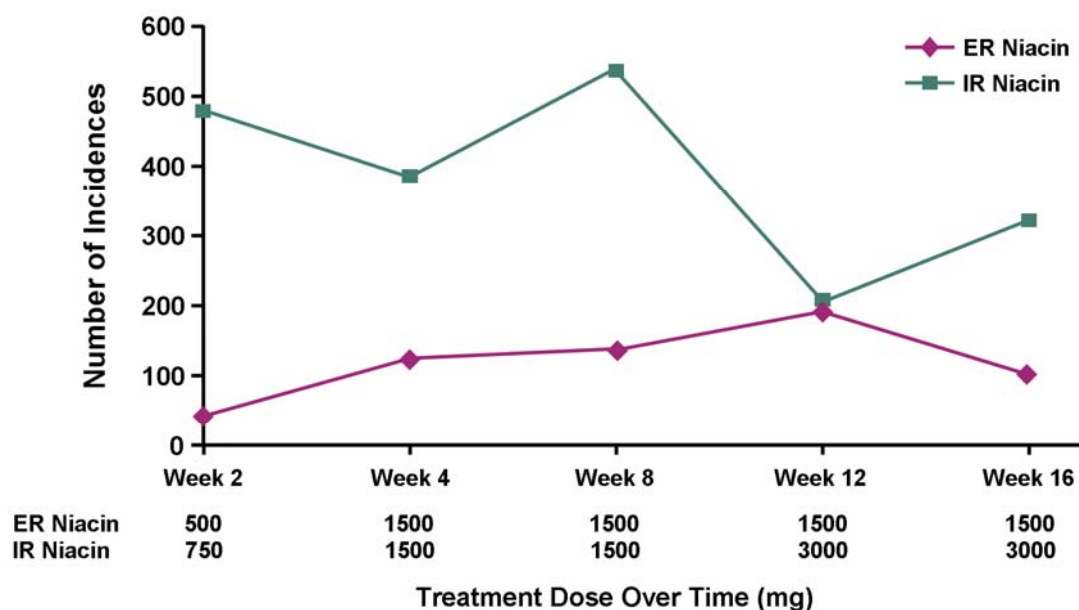
5.5   The Effect of Food and NSAIDs on Niacin-Induced Flushing

5.5.1   Food

Administration of niacin with food increases its overall bioavailability, but delays the rate of absorption of niacin.[36] A delayed rate of niacin absorption decreases its peak plasma concentration and may therefore mitigate flushing associated with the drug. Decreasing peak plasma concentrations appears to be one of the advantages of approved and commercially available ER niacin products such as Niaspan® and Advicor®.

The effect of food on niacin-induced flushing was explored in Studies AP-ADF-101 and AP-ADF-107, as described in Section 5.4.1, and in Study AP-ADF-102 (see Section 6.2.1.1) where a high-fat, high-calorie meal was shown to significantly reduce the disliking effects of niacin.

However, outside of the realm of controlled, clinical abuse liability studies, it is common practice for recreational opioid abusers to fast prior to dosing.[38] Thus, it would be contrary to prevailing habits for prospective abusers to proactively plan to eat a meal prior to swallowing excess doses of Acurox® Tablets to get high. Opioid abuse research suggests that the rate of rise in plasma concentration of an opioid is directly related to the quality and intensity of the euphoria, and to the reinforcement that occurs. However, eating prior to taking Acurox® Tablets reduces maximum oxycodone plasma concentration and delays the time to maximum plasma concentration from 1.3 to 2.9 hours, compared to the fasted state, as demonstrated in Study AP-ADF-108 (see Section 3.7). In addition, eating a meal involves planning and delay that is uncharacteristic of recreational abusers with impulsive needs for immediate gratification.[38]

In summary, while ingesting a meal is a theoretical strategy to ameliorate niacin-induced disliking effects, doing so has perceived and potentially real disadvantages for abusers in that it may not work consistently, requires pre-planning, and may delay or reduce opioid-induced gratification.

5.5.2   Non-steroidal Anti-Inflammatory Drugs (NSAIDs)

Administration of NSAIDs including aspirin prior to niacin ingestion also has the potential to mitigate some, but not all, of the flushing associated with niacin.

In one randomized, double-blind study, 42 healthy subjects received aspirin 325 mg, aspirin 650 mg, and placebo for 4 consecutive days. On the fourth day, subjects also ingested 500 mg of immediate release niacin 30 minutes after taking aspirin or placebo. Intensity of flushing, headache, pruritus, tingling, and warmth was assessed using a 10 cm visual analogue scale. Sixty percent of patients flushed when taking 500 mg of IR niacin alone for 4 days, versus 41% and 29% taking the same dose of niacin with 325 mg and 650 mg of aspirin, respectively.[39] In a literature survey conducted to explore the utility of aspirin in preventing niacin-related flushing, 325 mg of aspirin or 200 mg of ibuprofen taken with 500 mg of IR niacin decreased flushing in healthy subjects by 30%. In a third study, 22 healthy volunteers were randomized in a double-blind, crossover design to receive crystalline (IR) niacin 500 mg preceded by either placebo, aspirin 165 mg, aspirin 325 mg, or ibuprofen 200 mg administered 30 minutes prior to the niacin. Across all subjects who

experienced flushing, only aspirin 325 mg had a statistically significant reduction. When subjects experiencing the worst symptoms of flushing were analyzed separately, aspirin 325 mg was the most effective, followed by aspirin 165 mg and ibuprofen 200 mg.[40] In the latter study, the NSAID was administered 30 minutes before taking niacin. Data from controlled clinical trials show that the optimum effect is observed when subjects are pre-treated with aspirin at least 30 minutes prior to ingestion of niacin.[31] As with food, this requires planning in advance and delayed gratification, which is not characteristic of the behavior of recreational abusers.

Moreover, flushing with niacin is not completely mitigated by co-administration of an NSAID. Although tolerance developed over repeated administration, 125-250 mg of IR niacin administered 3 times daily caused flushing in 73% of patients despite allowing the use of 325 mg of aspirin. Finally, as noted in multiple references, administration of aspirin or NSAIDs such as ibuprofen (Advil®, Motrin®), naproxen (Naprosyn®), or indomethacin (Indocin®) can reduce, but do not eliminate flushing.[41]

Finally, the Summary Basis for Approval of Niaspan® indicated that flushing occurred in the majority of patients taking lipid-lowering doses of niacin despite prophylactic treatment with food and NSAIDs.[36]

In summary, pre-medication with an NSAID 30 minutes or more before ingesting Acurox® Tablets would be required by an abuser to help mitigate niacin-induced flushing associated with excessive oral intake of Acurox® Tablets. However, it would be contrary to an abuser's usual habits to proactively pre-medicate prior to swallowing excess doses of an opioid, including Acurox® Tablets. Furthermore, the preponderance of literature suggests that NSAIDs do not completely mitigate niacin-induced flushing.[42]

5.6   Safety of Niacin in Clinical Trials

There were 3 groupings included in the Integrated Summary of Safety (ISS) in the Acurox® NDA requested by the FDA during the Pre-NDA Meeting:

- Phase 1 Pharmacokinetic Studies
- Phase 2 and 3 Controlled Studies
- Abuse Liability Studies

The Phase 1 studies pooled in the NDA (AP-ADF-104, AP-ADF-108, and AP-ADF-109) are not presented in this Briefing Document. The studies included 94 healthy volunteers. In these studies no deaths or SAEs were reported. One subject taking Acurox® Tablets 5/30 mg in AP-ADF-108 experienced TEAEs unrelated to niacin (dyspnea, headache, and dizziness), and discontinued from the study. There were no concerns identified by FDA regarding these studies in the Complete Response Letter.

At the request of FDA, Studies AP-ADF-103 and AP-ADF-105, were pooled in the NDA but are separated in this Briefing Document for ease of analysis due to differences in study population (healthy volunteers vs. pain patients), sample size (n=22/group vs. n=134-136/group), and duration of treatment (10 days vs. 48 hours). The data obtained from the pivotal safety and efficacy study (AP-ADF-105) is most representative of the safety in the intended pain population.

The safety observed in the abuse liability studies is briefly summarized including the three studies of oral abuse (102, 111, 114) and one study (106) with nasal abuse. All of these studies were conducted in non-dependent recreational abusers who were otherwise healthy. This review of safety does not include a complete analysis of Study 114, which is pending.

No safety concerns about Acurox® Tablets have been expressed by the FDA except for the incidence of flushing in subjects or patients taking 60 mg doses of niacin with oxycodone HCl (i.e., the proposed recommended dose of niacin included in 2 x Acurox® Tablets 5/30 mg or 2 x Acurox® Tablets 7.5/30 mg). Therefore, the focus of this section is on flushing.

Flushing occurs as a common, well documented, self-limiting side effect of niacin when administered in excess of nutritional needs. Flushing is defined as a superficial skin sensation manifested by 1 or more of the following 4 symptoms – warmth, redness, tingling and itching.[36] Itching is also a well-recognized symptom associated with opioid agonists[28] believed to occur from the release of cutaneous histamine and likely to confound the precise etiology of skin sensations occurring as a result of niacin-opioid combinations. Tingling is a component of flushing that is coded to paraesthesia in the MedDRA coding system. Niacin does not cause paraesthesia related to neural toxicity, or any adverse effects on the nervous system.

5.6.1   *Phase 2 and 3 Controlled Clinical Studies*

Safety data from Studies AP-ADF-103 and AP-ADP-105 were reported together in the NDA at the request of the FDA for the NDA. These studies had a number of differences in population and study design and are presented separately in this document. There were no deaths or SAEs in these studies.

Study 103 was a trial in healthy volunteers examining the effects of niacin over time and when the dose is increased. The groups were taking 5/0 mg, 5/30 mg, and 5/60 mg during the treatment. Niacin-related symptoms reported during the study are provided in Figure 4, and suggest that a small amount of flushing and a substantial amount of pruritus occurs with oxycodone.

Figure 4.   Incidence of Flushing, Pruritus, and Paraesthesia in Study AP-ADF-103
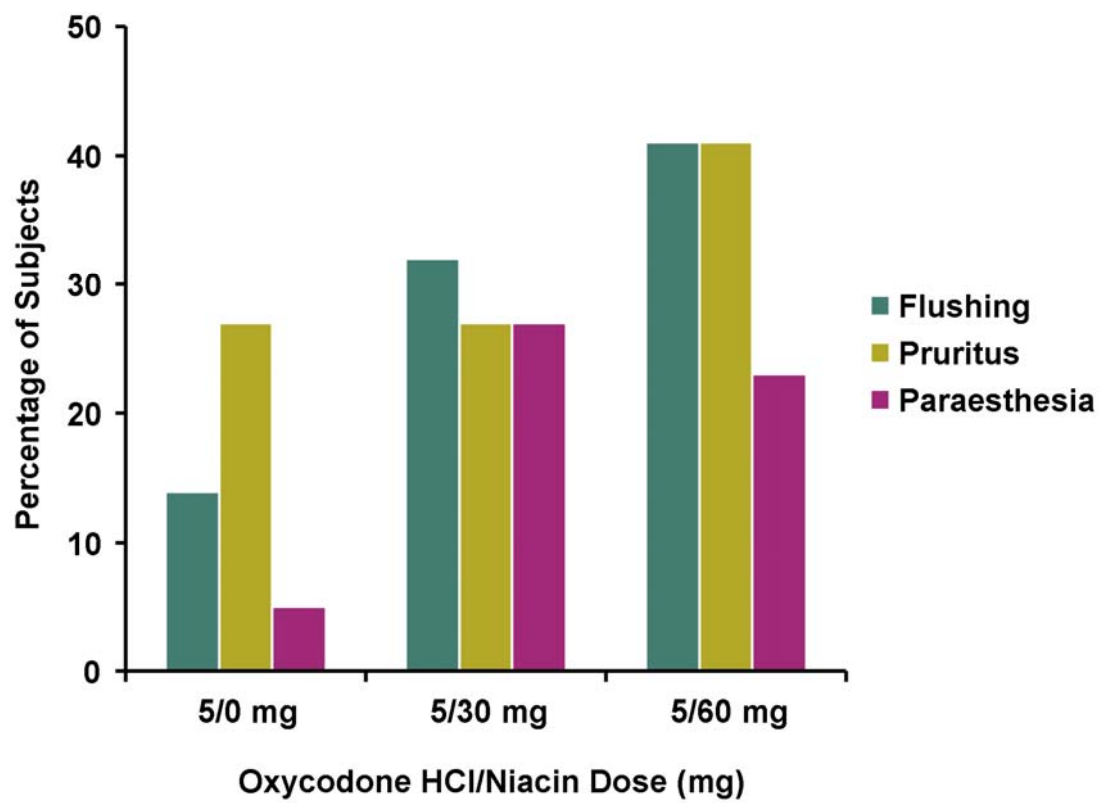
Study 105 was the definitive efficacy and safety trial of patients with moderate to severe post-operative pain. It compared two doses of Acurox® Tablets (2 x 5/30 mg and 2 x 7.5/30 mg) to placebo. It was conducted in a pain population, and was the best estimate of the effects of niacin on the intended population. There were no deaths or SAEs in either of these studies. Niacin-related symptoms reported in the study are provided in Table 5.

Table 5.   Treatment-Emergent Adverse Events Possibly Related to Niacin in ≥3% of Subjects in the Safety Population (Study AP-ADF-105)

Treatment-Emergent Adverse Event	Placebo (N=136)	Acurox® 2 × 5/30 mg (N=135)	Acurox® 2 × 7.5/30 mg (N=134)
	n (%)	n (%)	n (%)
Flushing	2 (1.5)	22 (16.3)	15 (11.2)
Pruritus	1 (0.7)	17 (12.6)	13 (9.7)
Pruritus generalized	1 (0.7)	8 (5.9)	10 (7.5)
Feeling hot	1 (0.7)	6 (4.4)	5 (3.7)
Paraesthesia	0	4 (3.0)	3 (2.2)
Hyperhidrosis	0	4 (3.0)	1 (0.7)

The most commonly reported niacin symptom in Study 105 (n=405) was flushing. Flushing occurred in 16.3% of subjects receiving two Acurox® Tablets 5/30 mg (n=135), 11.2% of subjects receiving two Acurox® Tablets 7.5/30 mg (n=134), and 1.5% of subjects receiving placebo (n=136). It is not possible to distinguish the amount of flushing that may have occurred from oxycodone compared to niacin in the study because there was no oxycodone only arm. All flushing events were mild to moderate in intensity, most began within one hour of the dose and rapidly resolved. There were 25 instances of flushing after the first dose, and no more than 5 after each of the subsequent doses. This suggests that flushing is not generally recurring at proposed recommended doses of Acurox® Tablets and occurs mostly after the first dose.

Other events possibly related to niacin occurring in <3% of subjects in any treatment group included feeling hot and cold, pyrexia, burning sensation, erythema, rash, rash generalized, skin burning sensation, urticaria, hot flush, and skin discoloration.

Episodes of syncope and hypotension in Study 105 were likely related to oxycodone.

Six subjects in the active drug treatment arms of Study AP-ADF-105 withdrew from the study. However, no subjects discontinued treatment for flushing or any other events likely related to niacin. The adverse events leading to discontinuation were reviewed for safety, and to assess if niacin may have contributed to the events. One subject discontinued for arthralgia unrelated to study drug, and one was discontinued for urticaria. The rash or redness known to occur from flushing raised the concern that the urticaria could be a flushing-related response. This is unlikely for several reasons. It occurred approximately 3 hours following the fifth dose of Acurox®. Flushing typically occurs within one hour after the dose.[43] The subject had a history of allergic rhinitis and allergies to bee stings and sulfa drugs. The urticaria was treated with an anti-histamine, and quickly resolved. Other events

leading to discontinuation included vomiting, hypotension, and bradycardia which are known effects of oxycodone and are not typical with the low dose of niacin administered in the study. The two discontinuations for hypotension occurred in subjects receiving two Acurox® Tablets 7.5/30 mg. Blood pressure changes from a low dose of niacin (e.g. 60 mg) are small, and rare.[44] Importantly, these events did not occur in any subject receiving only niacin in the development program at proposed recommended doses (i.e., 60 mg/dose).

These results indicate that in patients taking Acurox® Tablets at the proposed recommended doses for relief of moderate-to-severe pain, the level of flushing experienced is not harmful, and is not of sufficient intensity or duration to cause patients to discontinue taking their pain medication. Subjects stayed in the study and continued to obtain pain relief without discontinuing due to any AE associated with niacin. There was no evidence that the niacin-related AEs were associated with any lasting harmful effects consistent with the widely held view that flushing symptoms are clinically benign.

5.6.2   Abuse Liability Studies

5.6.2.1   Oral Abuse Liability Studies

The oral abuse liability studies were an opportunity to explore the safety of niacin in Acurox® Tablets at doses likely to be used by abusers. Over 100 healthy adult recreational drug abusers were exposed to excessive oral doses of Acurox® Tablets up to 80 mg of oxycodone HCl and up to 600 mg of niacin in abuse liability studies AP-ADF-102, AP-ADF-111 and AP-ADF-114 and completed the trial as detailed in Section 6.2.1.

There were no deaths or serious TEAEs reported during any study. The adverse events related to niacin and reported most frequently were flushing, pruritus, and paraesthesia. The events increased with dose. Flushing was noted in at least 60% of fasted subjects at doses of ≥240 mg. In the 114 study, skin burning sensation and skin warm were noted as common niacin-related events along with flushing and pruritus. There were no clinically relevant effects of these events on vital signs, and no other safety issues were reported.

5.6.2.2   Nasal Abuse Liability Study

A total of 15 healthy adult recreational drug abusers were administered up to 2 crushed Acurox® Tablets 7.5/30 mg intranasally in Study AP-ADF-106 as detailed in Section 6.2.2.1. There were no deaths or serious TEAEs recorded in this study. One subject discontinued from the study as the result of a moderately severe headache which occurred after nasal intake of ½ of a crushed Acurox® Tablet. Adverse events in this study that were increased with crushed Acurox® compared to crushed Roxicodone® and oxycodone HCl powder were nasal irritation (nasal discharge, nasal irritation, rhinitis) and flushing. Flushing occurred in 62% of subjects when Acurox® was crushed and snorted. These events were not related to any clinically relevant changes in vital signs and raised no safety concerns.

5.6.3   Laboratory Findings

There were no apparent treatment-related effects observed for any laboratory parameter in any individual study submitted with the NDA. There were isolated occurrences of

out-of-range laboratory values; however, no apparent treatment-related effects were observed for any laboratory parameter in Studies 103 and 105.

5.6.4   Vital Signs

In the pooled Phase 2 and 3 Controlled Studies (Studies 103 and 105), no treatment-related effects related to niacin on vital signs were observed. Mean values were similar in the total Acurox® Tablets group and the placebo group at both baseline and end of treatment.

5.7   Niacin Summary

5.7.1   Safety

The safety of Acurox® Tablets has been evaluated in a comprehensive clinical program in which 565 subjects participated in studies where Acurox® Tablets were orally administered at proposed recommended doses. No deaths or SAEs were reported in any clinical trial of Acurox® Tablets, and only 9 subjects discontinued from a clinical trial because of AEs.

The most robust safety information for the intended population with pain comes from Study 105. The safety of Acurox® Tablets in recreational abusers swallowing quantities higher than proposed recommended doses was demonstrated in the abuse liability studies. The safety conclusions are as follows:

- The 60 mg dose of niacin in the proposed recommended analgesic dose of Acurox® Tablets is safe and well tolerated in patients with moderate to severe pain.

- In the intended (pain) population, in Study AP-ADF-105 at least 84% of patients did **not** experience flushing. Flushing may occur in a small number of patients (at an anticipated rate of 10-15% more than placebo). Flushing is a benign potential effect that will be clearly identified in the Acurox® Tablets product labeling for the patient and prescriber.

- In abuse liability studies conducted with Acurox® Tablets, 240 mg and 480 mg doses of niacin were disliked, but safe, when administered with 40 mg and 80 mg of oxycodone HCl, respectively. The well established safety record of niacin at 240 mg and 480 mg daily doses is documented from studies of patients being treated chronically for dyslipidemias at niacin doses greater than 1000 mg per day.

- Flushing and other niacin-related TEAEs increased in frequency when given at doses higher than the proposed recommended dose of Acurox® Tablets.

- Pruritus is related to niacin and also occurs commonly with oxycodone HCl alone.

- Niacin-related TEAEs were not associated with clinically important changes in vital signs or any laboratory parameters.

- The TEAEs when crushed Acurox® Tablets were administered intranasally were related to nasal irritation with a possible systemic and/or local effect from niacin.

5.7.2   *Other Niacin Attributes in Acurox® Tablets*

- Niacin does not interfere with the analgesic efficacy of Acurox® Tablets.

- The 60-mg dose of niacin is rapidly eliminated following oral ingestion with a half-life of 20-45 minutes. The dose of niacin is essentially cleared prior to administration of the next dose (5-7 half lives with a q6h dosing interval).

- The 60 mg dose of niacin in the proposed recommended analgesic dose of Acurox® Tablets is similar to the amount in many foods and over-the-counter nutritional supplements. This low dose of niacin has no known pharmacodynamic or pharmacokinetic interactions with other drugs or concurrent disease states.

- Administration of niacin with food or an NSAID, such as aspirin or ibuprofen, may mitigate the flushing response of niacin in some individuals.

6.   ACUROX® TABLETS DEVELOPMENT PROGRAM

The clinical development program for Acurox® Tablets consisted of 11 studies, including:

- 3 PK and bioequivalence studies of Acurox® Tablets in healthy subjects (summarized in Section 3.7; AP-ADF-104, AP-ADF-108, AP-ADF-109);
- 2 safety/tolerability studies of niacin only (i.e., no oxycodone HCl) in healthy subjects (summarized in Section 5.4.1; AP-ADF-101 and AP-ADF-107);
- 1 safety/tolerability study of niacin with and without oxycodone HCl in healthy subjects (summarized in Section 5.4.1; AP-ADF-103);
- 3 oral abuse liability studies in healthy subjects with a history of non-dependent, recreational opioid abuse (summarized in Section 6.2.1; AP-ADF-102, AP-ADF-111, AP-ADF-114);
- 1 intranasal abuse liability study in healthy subjects with a history of non-dependent, recreational opioid abuse (summarized in Section 6.2.2; AP-ADF-106); and
- 1 pivotal safety and efficacy study in patients with moderate-to-severe post operative pain (summarized in Section 6.1; AP-ADF-105).

Ten of these 11 studies were included in the original NDA. One additional abuse liability study (Study AP-ADF-114) was initiated after the receipt of the Complete Response Letter to confirm the results of Study AP-ADF-111, and has recently been completed. A total of 565 subjects participated in clinical studies in which Acurox® Tablets were orally administered at proposed recommended doses.

In addition to the clinical studies, 2 laboratory studies were conducted to assess the intravenous abuse deterrent properties of Acurox® Tablets (Section 6.2.3).

6.1   Analgesic Efficacy

The FDA agreed that a single clinical study would be sufficient to demonstrate the safety and analgesic efficacy of Acurox® Tablets. Study AP-ADF-105 was conducted pursuant to an FDA agreed Special Protocol Assessment. Since it met the pre-defined analgesia end-points, the positive outcome of the study is not in doubt and it is not the subject of this Advisory Committee meeting. It is presented in summary form for completeness only.

Efficacy data from Study AP-ADF-105 are summarized below; safety and tolerability data are summarized in Section 5.6.1.

The study was a randomized, double-blind, placebo-controlled, multicenter, repeat-dose study in adult subjects with moderate to severe postoperative pain following bunionectomy surgery. Each subject received 2 Acurox® Tablets 5/30 mg or 7.5/30 mg (equivalent to 10 or 15 mg of oxycodone HCl and 60 mg niacin per dose) or matching placebo every 6 hours (irrespective of rescue medication use) for 48 hours. Ketorolac tromethamine was available as a rescue medication. The primary efficacy outcome was the time-weighted Sum of Pain Intensity Differences (SPID) over the 48-hour interval following the initial dose of study medication ($SPID_{48}$). Pain intensity was assessed using a 100 mm visual analog scale. Comparisons of each Acurox® Tablet dose level to placebo were made in a nested manner (higher dose first).

A total of 405 patients aged 18-77 years old (mean 41.8 years) were randomized; 135 patients in the Acurox® 2 × 5/30 mg group, 134 patients in the Acurox® 2 × 7.5/30 mg group, and 136 patients in the placebo group. The study population was primarily female (88.6%) and Caucasian (75.8%).

Both dosages of Acurox® Tablets demonstrated clinically meaningful and statistically significant superiority to placebo as measured by $SPID_{48}$.

The results for the primary efficacy variable ($SPID_{48}$) are summarized in Table 6.

Table 6.   Primary Endpoint Results from Study AP-ADF-105 - ITT Population

Variable Statistic	Placebo (N=136)	Acurox® 2 × 5/30 mg (N=135)	Acurox® 2 × 7.5/30 mg (N=134)
Sum of Pain Intensity Differences[a] from 0 to 48 Hours ($SPID_{48}$; primary efficacy variable)			
Mean ±SEM	604.5±96.5	998.5±94.9	1225.0±97.5
p-value vs placebo[b]	NA	0.0001	<0.0001

NA = not applicable; SEM = standard error of the mean.
[a] Pain Intensity Differences were calculated as Baseline PI minus post-Baseline PI.
[b] P-values are from an analysis of covariance model with treatment group and site as fixed effects and Baseline PI as the covariate.

6.2   Abuse Liability Clinical Studies

Clinical trials to evaluate abuse liability (i.e., to assess the potential of a drug product to limit or impede abuse), along with regulatory control of drugs with abuse liability through classification are important components of drug control policy and are intended to help minimize non-medical use.[45] An evolving body of literature concerning the study design and methodology for abuse liability studies has been published over the past few decades, and has helped FDA in preparing a draft Guidance for Industry titled "Assessment of Abuse Potential of Drugs." This FDA draft guidance document was distributed for public comment in January 2010 after all Acurox® Tablet clinical studies were either completed or, in the case of Study AP-ADF-114, in progress.[46]

Jasinski has written a comprehensive review of the evolution of opioid abuse liability assessment in humans.[47] More recently, the primary features of a classic "acute dose-effect comparison abuse liability trial" have been detailed by Griffiths and colleagues.[48] These studies are considered to be highly predictive of the abuse potential of a drug in recreational drug abusers.[49]

Typically, these studies involve the single-dose administration of each drug in a double-blind, randomized fashion using a complete crossover design. The profile of the acute effects of the test drug is compared to that of placebo and the reference drug.[50] Assessments are conducted prior to each dose administration and at multiple time points after dosing to develop a subjective effects profile (i.e., effects over time) for each assessment and each drug administered. Several assessments are typically used, the most important of which is the assessment of "drug liking." This measure has face validity and is the most reliable

measure of the likelihood of abuse. Visual analog scales are frequently used in this assessment, and these can be unipolar (e.g., ranging from like 'not at all' to 'like very much') or bipolar (e.g., ranging from 'dislike very much' to 'like very much'). Other assessments that correlate well with liking include assessments of good effects and bad effects, the degree to which the subject would like to take the drug again, and estimated street value. These latter assessments reflect the likelihood that drug-taking behavior will change as a result of the liking or disliking of the drug. Changing the behavior of misuse or abuse is the primary goal of introducing drug products designed to limit or impede abuse.

Assessments are made serially to obtain data over time after drug intake; and they should also be obtained after the drug's effects have dissipated, to obtain an assessment of the overall experience of the drug in the absence of any of its subjective effects. It is also recommended that abuse liability studies include measurements of some relevant dimension of biologic activity (e.g., behavioral performance as described above, observed-rated assessments, or physiologic measures such as pupillometry in the case of opioids).[48] It is important to note that no single assessment is able to completely characterize a product's potential for abuse;[45,50] rather, multiple measures that bear on abuse potential need to be evaluated, and the sum of evidence evaluated as a whole.[50]

Abuse liability studies are typically conducted in subjects with a history of abuse of drugs in the same class as the test drug,[48] but who are not dependent at the time of study enrollment.[50] Subjects with a history of recreational use can rely on their prior experience to provide meaningful ratings of the study drugs' subjective effects.[48] This subject population is most at risk for abusing the drug, and therefore is the most 'face valid' population in which to assess the abuse liability potential of a new drug among drug abusers. Ideally, study entry criteria would require these subjects to pass a discrimination test, in which they should be able to reliably discriminate between the positive control and a placebo in terms of pharmacologic effects, and should report that they "like" the effects of the positive control substantially more than the effects of the placebo.[50] For ethical reasons abuse liability studies have not been performed in opioid-naïve people who might be considering non-medical use of prescription opioids. However, it is reasonable to conclude that this population would also be discouraged from initiating use or from repetitive use by a product that was known to be generally disliked when swallowed in excess doses compared to other readily available opioids.

The generally accepted design elements, endpoints, and methods for assessing endpoints have evolved as noted above, and have culminated in the FDA's draft Guidance for Industry for the Assessment of Abuse Potential of Drugs. This draft document is in the public comment stage of development and includes the following key elements proposed for conducting clinical abuse liability studies are:

- Controlled, in-patient, clinical research setting to conduct the study
- Cross-over study design
- Double-blind, double-dummy placebo, and positive comparator controls
- Inclusion of co-primary endpoints and secondary endpoints of interest
- Study population of recreational drug abusers

Proposed outcome measures most directly related to the likelihood of abuse are:

- Ratings of liking ("Do you like the drug?") and other subject-rated effects
- Determining the subjects' disposition to take the drug again
- Drug identification (that is, subjects are able to categorize the effects of the test drug as similar to those of numerous classes of psychoactive drugs)

The clinical development program for Acurox® Tablets has benefited from consultation with the architects of the draft Guidance document; notably, numerous authorities in the field of human abuse liability evaluation and the FDA. The clinical and laboratory studies evaluating the abuse liability potential of Acurox® Tablets are summarized in the sections that follow.

6.2.1   *Evidence Supporting Oral Abuse Deterrence*

As previously stated, the ingestion of prescription opioids by the oral route of administration is the most prevalent route of abuse overall, and the route preferred by novices and new initiators of opioid abuse.[15,16,17] It is also the route of administration that results in the highest number of deaths.[13]

The oral abuse liability evaluation for Acurox® Tablets consisted of 3 prospective studies in over 100 recreational opioid abusers. Even though the program was designed and the studies were conducted prior to release of the Draft Guidance in January 2010, these studies are consistent with the design and execution principles for abuse liability studies presented in the Draft Guidance. These studies were: (1) AP-ADF-102 a phase II dose ranging study that provided an opportunity to evaluate and optimize procedures in subsequent dose effect studies; (2) AP-ADF-111 that was designed with the benefit of results from Study 102, and (3) AP-ADF-114 that was designed to confirm the results of Study 111 using more rigorous design and analytical features and to evaluate a dose-response to excess oral doses of Acurox®. All 3 studies used the measures of abuse liability specified in the Draft Guidance document including:

- Ratings of liking/disliking (primary endpoint) and other subject-rated effects
- Take drug again assessments
- Drug identification (subject can categorize effects of test drug compared to others in the class)

Study AP-ADF-114 was initiated and completed after receipt of the FDA's Complete Response Letter to reconfirm the disliking caused by excess oral doses of Acurox® Tablets was both statistically significant and clinically meaningful. Similarities and differences between these 3 oral abuse liability studies are presented in Table 7.

Table 7.   Comparison of Design Features for the Three Acurox® Tablets Oral Abuse Liability Studies in Non-Dependent Recreational Opioid Abusers

Selected Study Parameters	Study Number (n= randomized subjects)		
	AP-ADF- 102 n = 25	AP-ADF-111 n = 30	AP-ADF-114 n = 49
Doses and Controls			
Placebo fasted		√	√
Positive Control – Oxycodone HCl 40 mg fasted	√	√	√
Positive Control - Oxycodone HCl 80 mg fasted			√
Test Drug – Niacin 240 mg fasted		√	
Test Drug – Oxycodone HCl /niacin 40/240 mg fasted	√	√	√
Test Drug – Oxycodone HCl /niacin 40/480 mg fasted	√		
Test Drug – Oxycodone HCl/niacin 40/600 mg fasted	√		
Test Drug – Oxycodone HCl/niacin 40/600 mg fed	√		
Test Drug – Oxycodone HCl/niacin 80/480 mg fasted			√
Outcome Measures			
Drug *liking* was a primary efficacy measure[1]			
Drug *disliking* was a primary efficacy measure (unipolar scale)	√		
Drug *disliking* using a Liking/Disliking (bipolar scale) was a primary efficacy measure		√	√
Treatment Enjoyment Assessment Questionnaire (TEAQ)	√	√	
Take Drug Again Assessment (TDAA)			√
Global Assessment of Overall Drug Liking			√
Measures of Drug Effect Typical of Abused Drug Class or Other Measures			
Tolerability Rating Scale (TRS)[2]	√		
Addiction Research Center Inventory (ARCI) - LSD dysphoria/somatic bodily discomfort scale	√	√	
Relevant physiological effects (pupillometry)	√	√	√

[1] The original Study AP-ADF-102 protocol submitted to the IND incorrectly identified drug liking as the primary efficacy measure. The Investigator's Study Report correctly analyzed drug disliking as the primary efficacy measure and this protocol oversight was identified in the final Clinical Study Report.

[2] Not a validated scale.

6.2.1.1   Study AP-ADF-102

Objectives

Study AP-ADF-102 was the initial oral abuse liability study in non-dependent recreational opioid abusers. Information gained from this study provided important insight into the disliking effects of niacin at higher than proposed recommended doses of Acurox® Tablets and provided information for the design and conduct of subsequent studies. Objectives of the study were to:

- assess dose response for niacin-induced flushing in combination with 40 mg oxycodone HCl
- evaluate the safety and tolerability of niacin-induced flushing following varying niacin doses in combination with 40 mg oxycodone HCl
- confirm the appropriate strength of niacin to use in the Acurox® Tablets formulation of oxycodone HCl
- assess abuse deterrent potential of niacin
- evaluate the effect of a high fat meal on niacin-induced flushing

Methods

This was a single-center, randomized, double-blind, in-patient, 5-period crossover study conducted in healthy adult male and female subjects with a history of non-dependent, recreational opioid abuse. Each subject was randomized to a dosing sequence that included doses of niacin (0, 240, 480, and 600 mg) all administered in combination with 40 mg oxycodone HCl while the subjects were fasted. The final treatment for all subjects was 600 mg niacin in combination with 40 mg oxycodone HCl administered following a standardized high-fat meal.

The outcome measures for abuse liability were Drug Liking, Drug Disliking, and the Treatment Enjoyment Assessment Questionnaire. The maximum scale response to the question "Do you dislike the drug effect you are feeling now?" (the "Disliking Score") was the primary efficacy measure. The Disliking Score, the Liking Score, and Feel a Drug Effect Score (collectively known as the Drug Rating Questionnaire-Subject [DRQS]) were all scored by the subjects using a 29-point unipolar VAS. The TEAQ asked the subject to choose, among the study treatments received, which they would most enjoy taking again.

Additional assessments of subjective effects included the Addiction Research Center Inventory (ARCI), and an unvalidated Tolerability Rating Scale (TRS). The TRS asked subjects to rate their overall reaction to the study drug using a 5-point scale (from 0 = "no effect" to 4 = "intolerable, would never take again"). On each dosing day, vital sign measures, the DRQS, and the ARCI were assessed 0.5 hours before dosing (baseline, except for the ARCI) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 12 hours after dosing. The TEAQ was completed once after all treatments were administered; the TRS was completed 12 hours after administration of each dose of study drug.

Results

A total of 25 subjects were enrolled in the study; 24 subjects completed all 5 treatment periods.

As shown in Figure 5 for fasted subjects, 30 minutes after study drug administration, all doses of niacin (240, 480, and 600 mg) in combination with oxycodone HCl 40 mg produced significant ($p \leq 0.05$) Disliking Scores compared to oxycodone HCl 40 mg alone. This corresponds to the peak plasma concentration of niacin that occurs within 30-60 minutes of an oral dose. Mean differences from baseline in Disliking Scores in fasted subjects increased with increases in the niacin dose.

Figure 5.   Study AP-ADF-102 Drug Disliking Scores: Fasted Subjects

"Do you dislike the drug effect you are feeling now?"
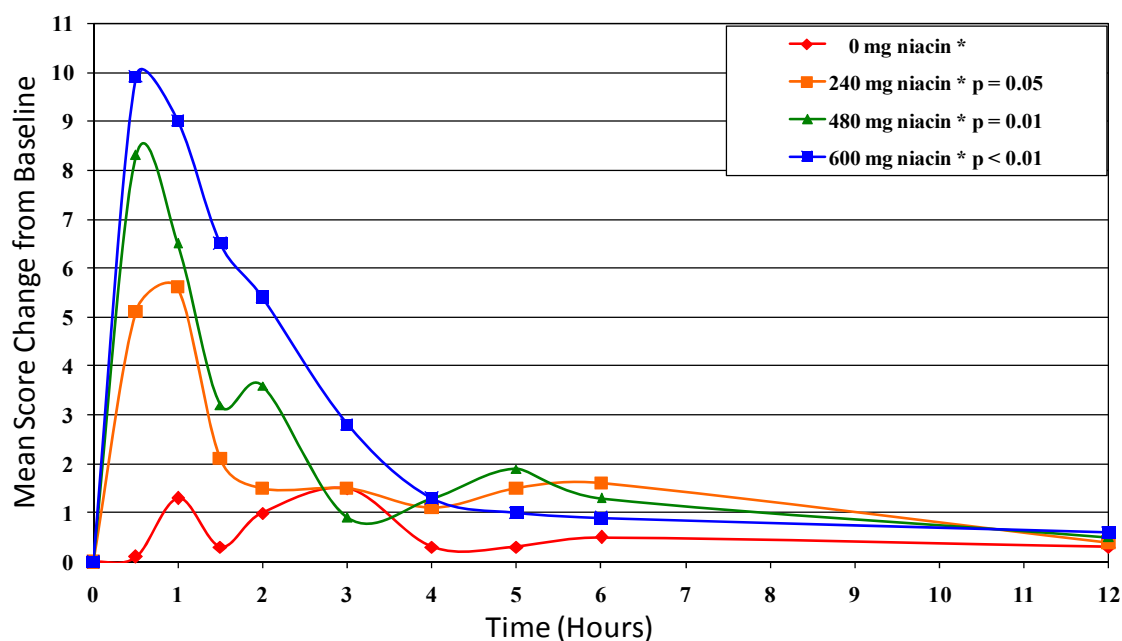
*All doses contained oxycodone HCl 40 mg.

Baseline score was established 0.5 hours prior to dosing and normalized to zero. For 0 mg niacin at 0.5 hour post-dose the actual value was -1.2, however for graphical clarity the 0.5-hour value is plotted as 0.

P-values were calculated using Dunnett's t-tests treating the 0 mg niacin with 40 mg oxycodone dose group as the control and comparing all other dose groups against it.

In fed subjects receiving niacin 600 mg in combination with oxycodone HCl 40 mg, there was no significant difference ($p = 0.75$) in mean Disliking Score change from baseline compared to fasted subjects receiving oxycodone HCl 40 mg alone (figure not shown). This is possibly due to the fact that food slows the rate of absorption of niacin, resulting in a lower peak plasma concentration of niacin. Peak concentration is associated with flushing and its component parts (tingling, itching, redness, and warmth).

However, as illustrated in Figure 6, in fed subjects, a high-fat meal delayed the time to the peak Drug Liking by approximately 2 hours and reduced the magnitude of peak Drug Liking compared to fasted subjects taking oxycodone HCl 40 mg alone. Liking instead of disliking is presented in Figure 6 to demonstrate the mitigation of the niacin disliking effects when administered with a high fat meal. While the results depicted in Figure 6 are not statistically significant, they indicate that attempts to counter niacin-induced disliking effects with food may also delay and possibly reduce liking effects typically experienced by abusers of oxycodone tablets.

Figure 6.   Study AP-ADF-102 Drug Liking Scores: Fasted versus Fed Subjects

"Do you like the drug effect you are feeling now?"
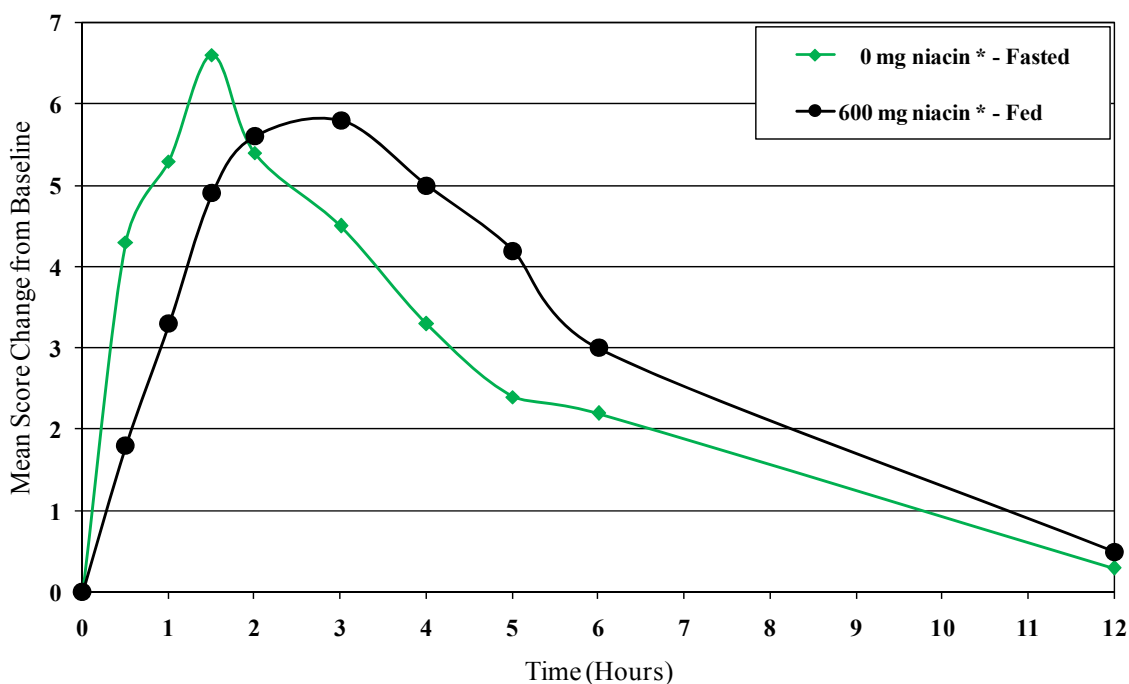
* All doses contained 40 mg oxycodone HCl
  Baseline Score established 30 minutes prior to dosing

In addition, the Disliking Score change from baseline during the first 3 hours following oral dosing with oxycodone HCl/niacin 40/600 mg was analyzed for fasted and fed subjects (figure not shown). During this 3-hour period, 70% (17 of 24) of fasted subjects disliked (positive Disliking Score change from baseline) the drug compared to 42% (10 of 24) of fed subjects. Despite the high-fat meal, 25% (6 of 24) of fed subjects experienced a maximum change in Disliking Score from baseline of greater than 5 during the 3 hours after dosing, indicating the niacin food effect does not reverse Drug Disliking in all subjects. While these results are not statistically significant, they indicate that disliking of niacin, even after food, may have the potential to limit or impede abuse in some opioid abusers.

The manner in which the TEAQ data were collected in this study makes interpretation difficult. The TEAQ was completed once by the subject after receiving the last dose of study

drug. Hence, the subject had to recall 5 drug experiences across 9 days in making his/her TEAQ assessment. Furthermore, the high fat meal condition was the last treatment for each subject rather than interspersed in random order. With these limitations, 10 subjects (41.7%) taking oxycodone HCl 40 mg with niacin 600 mg after consuming the high-fat meal and two subjects (8.3%) taking oxycodone HCl 40 mg alone in the fasted state reported these treatments as the ones they would most enjoy taking again. The next most frequent choice, "none of the drugs," was selected by 6 subjects (25%).

There were no significant differences between any of the oxycodone HCl 40 mg plus niacin treatments compared with the oxycodone HCl 40 mg alone treatment on the ARCI MBG (euphoria) or Lysergic Acid Diethylamide/Dysphoria Scale (LSD) (dysphoria) subscale scores (all $p > 0.05$). The Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) (sedation) subscale mean score difference in the niacin 480 mg with oxycodone HCl 40 mg group, compared to oxycodone HCl 40 mg alone (i.e., 0 mg niacin), suggested this dose of niacin reduced the sedative effect of oxycodone (-1.4; $p = 0.04$). There were no differences (all $p > 0.05$) in any of the ARCI subscale scores between fed subjects receiving niacin 600 mg with oxycodone HCl 40 mg and fasted subjects receiving oxycodone HCl 40 mg alone.

Results from the TRS showed that the proportion of fasted subjects reporting the drug "unpleasant and difficult to tolerate" or "intolerable and would never take again" was highest during treatment with oxycodone HCl 40 mg with niacin 600 mg. There was no difference between oxycodone HCl 40 mg with niacin 240 mg and oxycodone HCl 40 mg in the proportions of subjects reporting the treatment had "no effect" or was "easy to tolerate." The TRS also showed that subjects tolerated oxycodone HCl 40 mg with niacin 600 mg better when fed than when fasting.

Conclusions

The results of this study demonstrate that, in a fasted state, increasing doses of niacin administered in combination with oxycodone HCl 40 mg produced dose-dependent increases in Disliking Scores, all of which were statistically significant ($p \leq 0.05$) compared to oxycodone HCl 40 mg alone at the 30-minute time point. In fasted subjects, at 0.5 hours post dosing, there was a statistically significant difference in the mean DRQS dislike scores (the primary efficacy measure) between all study treatments with niacin (i.e., oxycodone HCl/niacin 40/240 mg, 40/480 mg, and 40/600 mg) compared to oxycodone HCl 40 mg alone.

Niacin-induced disliking of oxycodone was attenuated by a high-fat meal in most, but not all subjects. However, a high-fat meal also delayed by approximately 2 hours the time to maximum oxycodone liking effects and was associated with a lower mean Liking Score. These results led to the conclusion that excess oral doses of Acurox® Tablets may be unattractive to potential opioid abusers compared to equivalent excess doses of oxycodone HCl tablets alone (without niacin).

Learnings for Subsequent Studies

Study 102 examined the effects of a high-fat meal for the niacin 600-mg dose in combination with oxycodone HCl 40 mg. However, the fed arm was administered as the final treatment for all subjects in a non-blinded fashion outside of the double-blind, randomized design used

for all fasted treatment arms. This non-randomized evaluation of the effect of food should be considered when interpreting results from all of the rating scales.

The study design was not optimized for the TEAQ because subjects had too many potential choices (i.e., subjects could choose any 1 of 5 study drug treatments on 5 different treatment days or indicate "none of the treatments"). An optimal study design for the use of the TEAQ would have compared 2 drug treatments administered in random order on consecutive treatment days (as was done in Study AP-ADF-111).

The TRS was an assessment tool developed by Acura for guidance in establishing the appropriate dose of niacin to include in Acurox® Tablets when the drug product was appropriately used in patients with moderate-to-severe pain. It is not used to assess subject response in abuse liability studies. Because the TRS was a new, non-validated, non-calibrated assessment tool, results from this assessment were interpreted with caution and were not to be relied on to draw any firm conclusions relating to the relative efficacy of niacin in reducing the abuse liability of Acurox® Tablets. It was not used in subsequent studies since it was not a validated and accepted instrument for assessing abuse liability.

6.2.1.2   Study AP-ADF-111

Objectives

Procedures, assessment tools, and design elements were changed and/or modified from Study 102 and incorporated into a more rigorous oral abuse liability study in non-dependent, recreational opioid abusers (Study AP-ADF-111). Objectives of this 2-part study were to:

- Part 1: assess the effect of oxycodone HCl on niacin-induced disliking effects when oxycodone HCl is administered in combination with niacin
- Part 2: assess the abuse liability potential of 4 times the proposed recommended dose of Acurox® Tablets versus equivalent oxycodone HCl Tablet doses alone

Methods

This was a 2-part, single-center, randomized, double-blind, in-patient study of the abuse liability of Acurox® Tablets in 30 healthy adult male and female subjects with a history of non-dependent, recreational opioid abuse. The study design and doses administered in each part of the study are provided in Figure 7.

Figure 7.   Study AP-ADF-111 Design and Doses

Doses separated by 48 hours and administered in the fasted state
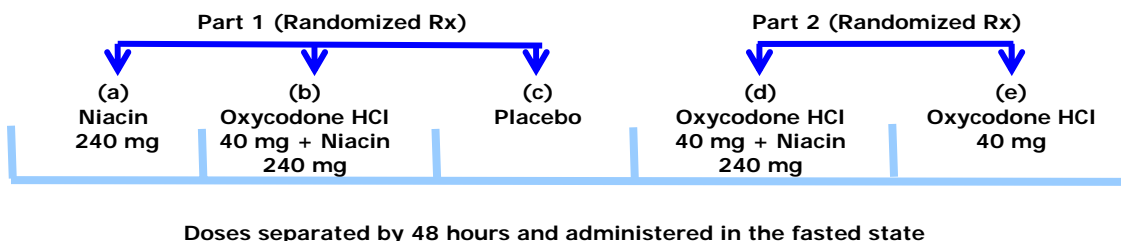
The outcome measures for abuse liability were drug Liking/Disliking as measured by a DRQS and the TEAQ. The items of the DRQS included the Liking/Disliking Score, using a 29-point bipolar VAS with scores ranging from "dislike an awful lot" to "like an awful lot"

with the midpoint of "15" labeled as "neither like or dislike," and the Feel a Drug Effect Score using a 29-point unipolar VAS with scores ranging from "not at all" to "an awful lot." The maximum response on the Liking/Disliking Score was designated as the primary efficacy variable. The TEAQ was assessed in Part 2 only for Doses "d" and "e." The single question asked was "Of the last 2 treatments, which would you enjoy taking again?"

Additional assessments included the ARCI and the Street Value Assessment Questionnaire (SVAQ) (Part 2 only). The single question on the SVAQ was "What would you pay for the drug you took yesterday if it was offered to you on the street?"

Pupillometry was used to measure the physiologic effects of oxycodone (i.e., oxycodone exposure).

Results from Part 1

A total of 30 subjects were enrolled and all 30 subjects completed the study.

As illustrated in Figure 8, the mean Dislike/Like score change from baseline (the primary efficacy variable) demonstrated the subjects' significant dislike (adjusted $p = 0.03$) of niacin 240 mg compared to placebo at 0.5 hour post-administration. Mean responses for placebo and the oxycodone HCl 40 mg/niacin 240 mg combination were compared to niacin 240 mg alone using Dunnett's test for multiple comparisons.

As expected from its rapid absorption and short half-life, the niacin-induced disliking effects manifested rapidly, reaching peak at 0.5 hour and diminishing thereafter. Beyond 0.5 hour after drug administration, oxycodone HCl 40 mg had limited effect on niacin-induced disliking. At the 1-hour observation and afterward, oxycodone attenuated niacin-induced disliking. Placebo showed little effect and had values consistently close to baseline. The effect of oxycodone on niacin did not overcome disliking in the first hour. However, liking did increase after that time as the effect of niacin waned, and the effect of oxycodone persisted.

Figure 8.   Study AP-ADF-111 Drug Dislike/Like Scores: Treatment Phase Part 1
"Do You Dislike or Like the Drug Effect You are Feeling Now?"
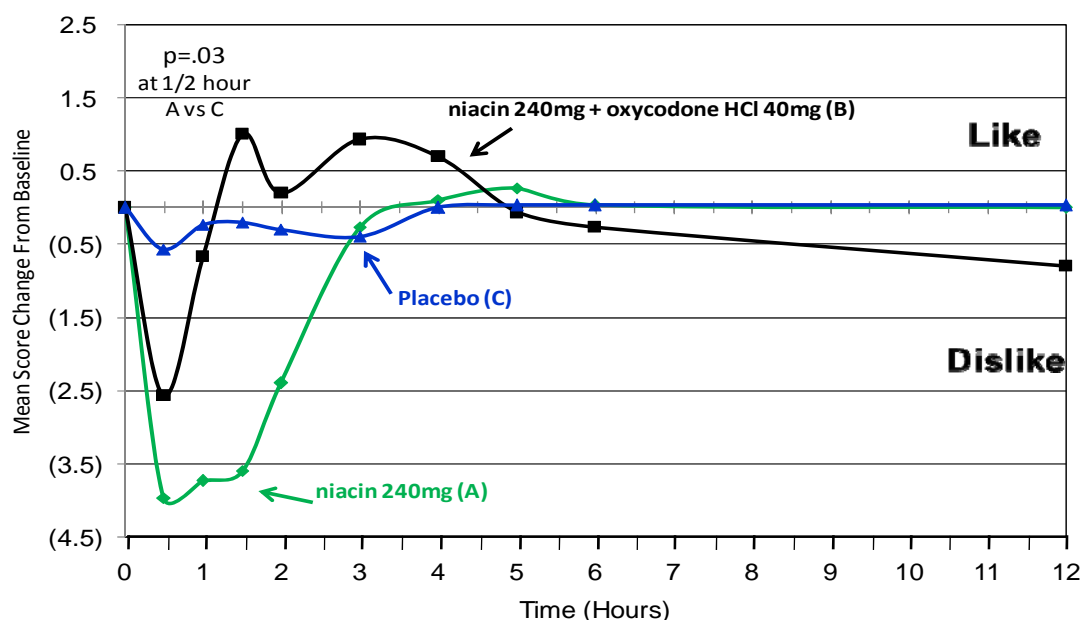
Note: Adjusted P-value was calculated using Dunnett's t-tests treating the niacin 240 mg group
as the control and comparing the other treatments against it.

Results from Part 2

As illustrated in Figure 9, the mean Dislike/Like score change from baseline (the primary
efficacy variable) versus time demonstrated that the combination of oxycodone HCl 40 mg
and niacin 240 mg (4 times the proposed recommended 2-tablet dose of Acurox® Tablets
5/30 mg) was aversive compared to oxycodone HCl 40 mg alone, as demonstrated by
statistically significant results in the Dislike/Like scores (p = 0.033) at 0.5 hour. The
0.5-hour time point was used for statistical analysis as it was the time of the maximum niacin
effect on oxycodone. At the 1-hour time point, the aversive effect of the combination of
oxycodone HCl 40 mg and niacin 240 mg had attenuated, and continued to decrease
thereafter. By the 3-hour time point, the Dislike/Like Scores for oxycodone HCl 40 mg
alone and for the combination of oxycodone HCl 40 mg and niacin 240 mg were essentially
the same.

There was a statistically significant and clinically meaningful difference in the TEAQ
assessment comparing Acurox® Tablets and oxycodone HCl tablets alone (without niacin).
Of the 30 subjects who completed the study, 23 (77%) preferred oxycodone HCl 40 mg alone
to oxycodone HCl/niacin 40/240 mg (p = 0.005).

In addition to significant Dislike/Like scores and the TEAQ results, there was a statistically
significant difference in the LSD/dysphoria scores (p < 0.01) between treatments.

The SVAQ score did not achieve statistical significance, but showed a trend indicating that
subjects would pay more for oxycodone alone than for Acurox® Tablets (p=0.097).
Subjective measures not achieving statistical significance included the Morphine-Benzedrine

Group/Euphoria (MBG) Scale scores measuring euphoria and the PCAG score measuring apathetic sedation. This suggests that the disliking associated with niacin is likely to be caused by its somatic side effects rather than by a blocking of the euphoric effects of oxycodone, as would be expected from the mechanism of action of niacin.

Figure 9.   Study AP-ADF-111 Drug Dislike/Like Scores: Treatment Phase Part 2

"Do You Dislike or Like the Drug Effect You are Feeling Now?"
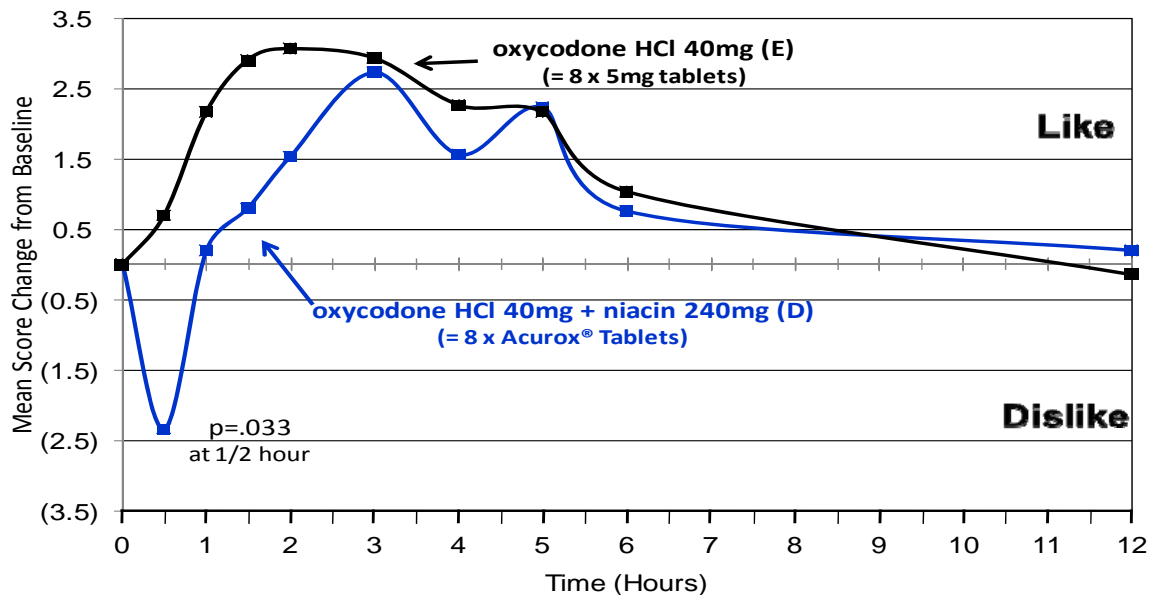
P-value was calculated using multivariate ANOVA treating oxycodone HCl 40 mg/niacin 240 mg as the control and comparing oxycodone HCl 40 mg alone against it.

Conclusions

Study 111 outcome measures directly related to the likelihood of abuse; ratings of Liking/Disliking (primary endpoint) and the TEAQ, were statistically significant. These results demonstrate that the niacin ingredient in Acurox® Tablets has the potential to limit or impede oral abuse of excess doses of Acurox® Tablets in a population of non-dependent, recreational opioid abusers. The disliking effects at 30 minutes with Acurox® were consistent with the TEAQ data showing that recreational opioid abusers preferred oxycodone HCl alone to Acurox® Tablets. The TEAQ data are a potential surrogate for real world deterrence.

The disliking effects of niacin wane by 3 hours post-dose, suggesting the possibility that some abusers may still consider taking excess doses of Acurox® Tablets to achieve a later pleasurable effect; however this behavior would not be consistent with results from the TEAQ. In addition, the statistically significant LSD dysphoria scores further support the TEAQ results.

6.2.1.3   Study AP-ADF-114

Objectives

Study AP-ADF-114 was conducted to confirm findings of Study AP-ADF-111, to apply a more rigorous experimental and analytical design, and to explore more than one potentially abused excess dose of Acurox® Tablets. Objectives of the study were to compare the relative abuse potential of 2 different doses of orally administered Acurox® Tablets to orally administered IR oxycodone HCl tablets in non-dependent recreational opioid users. Secondary objectives assessed the dose-response for relative abuse potential of 2 different doses of orally administered Acurox® Tablets, and the safety of high doses of Acurox® Tablets.

Methods

This was a single-center, randomized, double-blind, active- and placebo-controlled, in-patient, 5-way crossover study in healthy adult male and female subjects who were non-dependent recreational opioid users.

Each subject completed a Screening/Naloxone Challenge/Drug Discrimination Phase, a Treatment Phase with 5 dosing periods, and an End-of-Study Phase. Subjects who successfully completed all initial screening assessments and evaluations as outpatients returned to the study center as inpatients. A Naloxone Challenge was performed to ensure that subjects were not physically dependent on opioids, and a randomized and blinded Drug Discrimination Test was performed to ensure that subjects could differentiate between placebo and oxycodone, and that subjects "liked" the effects of oxycodone more than those of placebo.

Subjects who successfully completed the Screening/Naloxone Challenge/Drug Discrimination Phase entered the inpatient Treatment Phase and were randomized to 1 of 10 treatment sequences. During the Treatment Phase, subjects received each of 5 treatments according to their treatment sequence. The order of treatments within a sequence was determined using a Williams Design. Doses were separated by 48 (± 1) hours. The 5 treatments administered to each subject during the Treatment Phase included:

- Treatment A: oxycodone HCl/niacin 40/0 mg;
- Treatment B: oxycodone HCl/niacin 80/0 mg;
- Treatment C: oxycodone HCl/niacin 40/240 mg;
- Treatment D: oxycodone HCl/niacin 80/480 mg and;
- Treatment E: placebo (oxycodone HCl/niacin 0/0 mg).

Study 114 was not formally powered for any single analysis. However, power calculations for select analyses were performed assuming 40 completers, and assumptions based on the results of Study AP-ADF-111. The comparison of Acurox® Tablets 40/240 mg vs. oxycodone HCl 40/0 mg IR, using the AUEs for Drug Liking/Disliking, had power of at least 80%-90% assuming a mean difference of 22-25 h*mm and a standard deviation of the paired differences of 40-45 h*mm, based on a paired t-test for analysis and a significance level of 5%.

The doses of Acurox® Tablets evaluated in this study were selected to: (1) deliver doses of oxycodone that are believed to be most frequently abused in the real world and that achieve the liking and euphoria that abusers seek; (2) study the abuse-deterrent effects of the doses of niacin that would be ingested by an abuser who takes a sufficient number of Acurox® Tablets equivalent to a 40-mg or 80-mg dose of oxycodone HCl; and (3) determine if there is a dose-response for both liking of a 40-mg vs. 80-mg dose of oxycodone HCl and the abuse limiting effects of niacin.

The outcome measures for abuse liability were Drug Liking/Disliking, a Take Drug Again Assessment Questionnaire, and a Global Assessment of Overall Drug Liking. Pupillometry was used to measure the physiologic effects of oxycodone (i.e., oxycodone exposure).

A 100-mm bipolar VAS was used to assess: (1) Drug Liking/Disliking, anchored in the center with "neither like nor dislike" (score of 50), on the left with "dislike an awful lot" (score of 0) and on the right with "like an awful lot" (score of 100); (2) the TDAA; and (3) a Global Assessment of Overall Drug Liking.

The primary endpoint was the Drug Liking/Disliking VAS. The peak plasma concentration of niacin, and the corresponding niacin disliking effects, usually peak within 30-60 minutes after the dose. This was previously confirmed in AP-ADF-102 and AP-ADF-111. Consequently, to assess the immediate impact of Acurox® Tablets on oxycodone HCl liking, the peak disliking effect (E_{min}) and the effect (liking or disliking) at 30 minutes ($E_{0.5h}$) were selected as primary assessment parameters. Other primary assessment parameters were the areas under the effect (AUE) curve over the interval from time 0 to 1 hour (AUE_{0-1h}), from time 0 to 2 hours.(AUE_{0-2h}), and from time 0 to 3 hours (AUE_{0-3h}). These time intervals are measures of the persistence of the early disliking induced by niacin that is designed to disrupt the liking of oxycodone over a similar time interval.

The primary comparisons for the primary assessment parameters were:

- Treatment A (40/0 mg) vs. Treatment E (0/0 mg)
  (all primary assessment parameters except Emin)
- Treatment C (40/240 mg) vs. Treatment A (40/0 mg)
  (all primary assessment parameters)
- Treatment B (80/0 mg) vs. Treatment E (0/0 mg)
  (all primary assessment parameters except Emin), and
- Treatment D (80/480 mg) vs. Treatment B (80/0 mg)
  (all primary assessment parameters)

Raw p-values for these primary comparisons were adjusted for multiplicity using the Benjamini-Hochberg method[51] across the primary assessment parameters for the Drug Liking/Disliking VAS. The adjusted comparisons were used to assess the primary study objective. This allowed the simultaneous consideration of multiple endpoints to assess the primary objective while maintaining a false discovery rate of 0.05 for the primary comparisons.

Results

A total of 49 subjects were randomized into the Treatment Phase, and 47 subjects completed the study.

As illustrated in Figure 10, the mean Liking/Disliking score (the primary efficacy variable) versus time profile demonstrated that both doses of Acurox® Tablets (40/240 mg and 80/480 mg) were disliked as indicated by scores of < 50 on the VAS, and were lower than their respective IR oxycodone HCl dose. As noted in Table 8, all planned primary comparisons using the primary assessment parameters were statistically significant and in the expected direction. The peak disliking effect and effect at 0.5 hours (E_{min}, $E_{0.5h}$) demonstrated that the disliking effects of Acurox® Tablets peaked within 1 hour; the time frame associated with the peak liking effect (rapid high) that occurred with IR oxycodone doses. Assuming that a 10-point difference in the 100-mm VAS is clinically relevant, the magnitude of the differences for both doses of Acurox® Tablets evaluated by E_{min} (-10.4 and -14.1) and $E_{0.5h}$ (-18.7 and -34.8) are clinically relevant, and show a dose-response. The E_{min} for the 2 IR oxycodone only arms were similar to placebo, and tended to occur towards the latter half of the 12-hour assessment period. As indicated by the statistically significant differences for AUEs between both Acurox® Tablet doses and their respective IR oxycodone doses, the relative disliking effect is maintained over the first 3 hours following the dose.

As noted in Figure 10, even though the niacin effects wane over time, the peak liking effects of both Acurox® Tablet doses are delayed by 0.5 to 1.5 hours in a dose-dependent manner, and are significantly less than the peak liking of the corresponding IR oxycodone dose (6 points for the Acurox® Tablets 40/240 mg dose and approximately 10 points for the 80/480 mg dose). Finally, the validity of the study was confirmed (assay sensitivity) by the statistically significant differences in all primary assessment parameters comparing oxycodone HCl 40 mg to placebo and oxycodone HCl 80 mg to placebo.

Figure 10.   Study AP-ADF-114 Drug Dislike/Like Scores
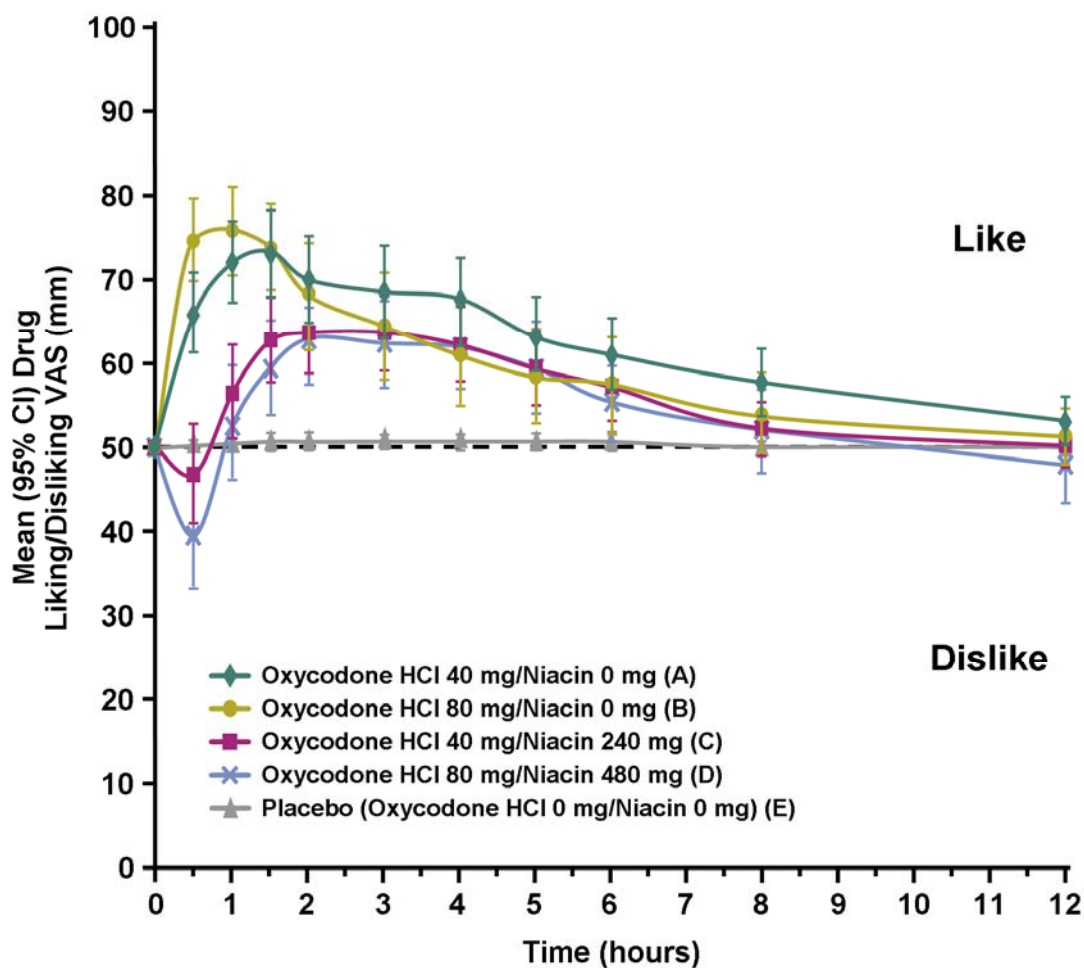
Table 8.   Summary of Primary Drug Liking/Disliking Parameters (Study AP-ADF-114)

| Parameter	Pairwise Comparisons	LSMean Difference (SE)	95% CI Difference	Unadjusted p-value[1]	Adjusted p-value[2]
AUE_{0-1h} (h*mm)	40/0 mg (A) v 0/0 mg (E)	13.2 (2.15)	8.9, 17.4	<.0001	<.0001
	40/240 mg (C) v 40/0 mg (A)	-13.2 (2.15)	-17.4, -8.9	<.0001	<.0001
	80/0 mg (B) v 0/0 mg (E)	18.7 (2.15)	14.4, 22.9	<.0001	<.0001
	80/480 mg (D) v 80/0 mg (B)	-23.1 (2.15)	-27.3, -18.8	<.0001	<.0001
AUE_{0-2h} (h*mm)	40/0 mg (A) v 0/0 mg (E)	34.8 (4.42)	26.1, 43.5	<.0001	<.0001
	40/240 mg (C) v 40/0 mg (A)	-23.8 (4.42)	-32.5, -15.1	<.0001	<.0001
	80/0 mg (B) v 0/0 mg (E)	41.1 (4.41)	32.4, 49.8	<.0001	<.0001
	80/480 mg (D) v 80/0 mg (B)	-37.2 (4.41)	-45.9, -28.5	<.0001	<.0001
AUE_{0-3h} (h*mm)	40/0 mg (A) v 0/0 mg (E)	53.3 (6.66)	40.1, 66.4	<.0001	<.0001
	40/240 mg (C) v 40/0 mg (A)	-29.2 (6.66)	-42.4, -16.1	<.0001	<.0001
	80/0 mg (B) v 0/0 mg (E)	56.6 (6.65)	43.5, 69.7	<.0001	<.0001
	80/480 mg (D) v 80/0 mg (B)	-40.6 (6.66)	-53.8, -27.5	<.0001	<.0001
$E_{0.5h}$ (mm)	40/0 mg (A) v 0/0 mg (E)	15.4 (3.12)	9.3, 21.6	<.0001	<.0001
	40/240 mg (C) v 40/0 mg (A)	-18.7 (3.12)	-24.8, -12.5	<.0001	<.0001
	80/0 mg (B) v 0/0 mg (E)	24.5 (3.12)	18.4, 30.7	<.0001	<.0001
	80/480 mg (D) v 80/0 mg (B)	-34.8 (3.12)	-40.9, -28.6	<.0001	<.0001
E_{min} (mm)	40/240 mg (C) v 40/0 mg (A)	-10.4 (2.54)	-15.4, -5.3	<.0001	<.0001
	80/480 mg (D) v 80/0 mg (B)	-14.1 (2.54)	-19.1, -9.1	<.0001	<.0001

[1]Pairwise comparisons unadjusted p-values are from a Linear Mixed Model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence.
[2]Pairwise comparisons adjusted p-values are completed using the Benjamini-Hochberg method
Note: Treatment groups per protocol and expressed as mg oxycodone HCl / mg niacin

As shown in Figure 11, there were statistically significant and clinically meaningful differences in the TDAA at all time points assessed (1, 2, and 8 hours) comparing both doses of Acurox® Tablets (40/240 mg and 80/480 mg) to their respective IR oxycodone doses without niacin.

Figure 11.   Study AP-ADF-114 Take Drug Again Assessment
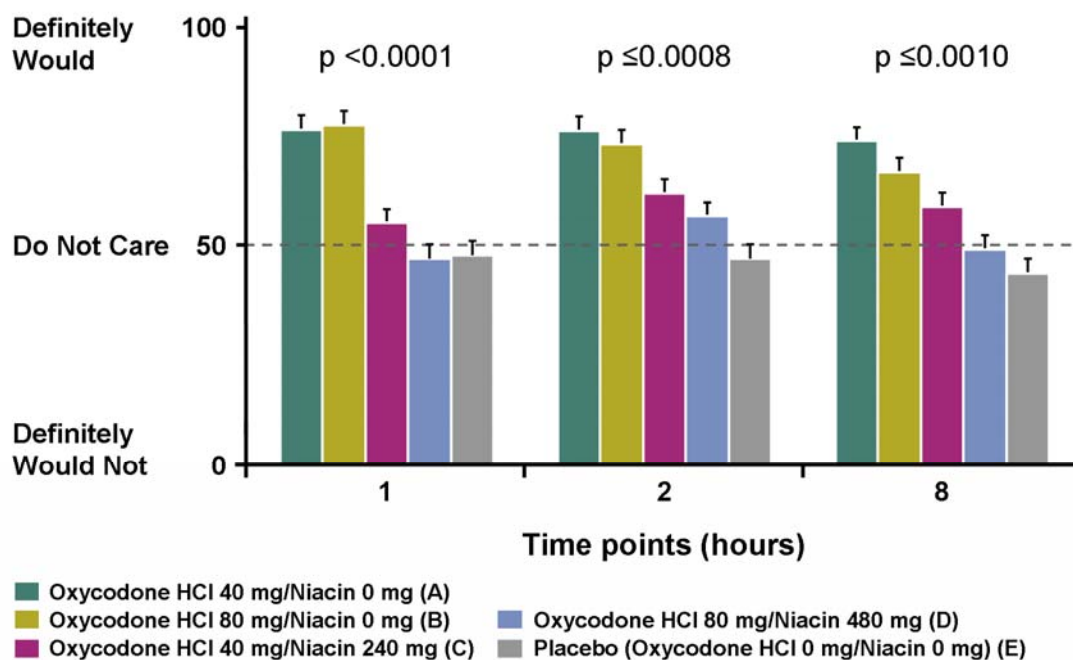
P-values at each time point compare Treatment C to Treatment A, and Treatment D to Treatment B. Bars are predicted means plus standard error.

As noted in Figure 12, the Global Assessment of Overall Drug Liking demonstrated statistically significant differences in overall drug liking at 12 hours comparing both doses of Acurox® Tablets (40/240 mg and 80/480 mg) to their respective IR oxycodone dose ($p = 0.0032$ for Acurox® Tablets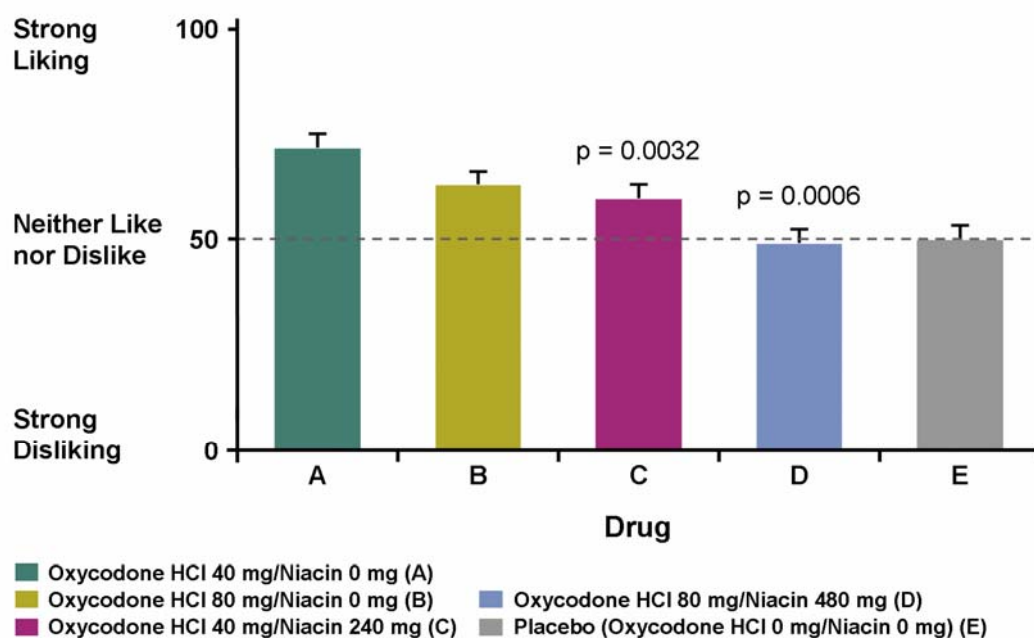 40/240 mg vs. oxycodone HCl 40 mg; $p = 0.0006$ for Acurox® Tablets 80/480 mg vs. oxycodone HCl 80 mg). The early disliking effects induced by niacin predicted later global effects.

Figure 12.   Study AP-ADF-114 Global Assessment of Overall Drug Liking

P-values compare Treatment C to Treatment A, and Treatment D to Treatment B. Bars are predicted means plus standard error.

Conclusions

The outcome measures directly related to the likelihood of abuse, ratings of Liking/Disliking (primary endpoint) and the TDAA demonstrated the oral abuse limiting properties of niacin at two excess oral doses of Acurox® Tablets in a population of non-dependent, recreational opioid abusers. These results are consistent with the two previous oral abuse liability studies conducted for Acurox® Tablets. Early disliking effects predicted later global measures of decreased abuse potential behavior. The TDAA data are a potential surrogate of community behavior. Recreational opioid abusers preferred excess doses of IR oxycodone without niacin to excess doses of Acurox® Tablets in a highly statistically significant and clinically meaningful manner.

6.2.2   *Evidence Supporting Nasal Abuse Deterrence*

6.2.2.1   **Study AP-ADF-106**

Objectives

Study 106 was performed to assess the human abuse liability, safety and comparative pharmacokinetics of intranasally administered crushed Acurox® (oxycodone HCl/niacin) Tablets compared to crushed Roxicodone® (oxycodone HCl tablets, USP) and oxycodone HCl powder in non-dependent, recreational opioid abusers.

Methods

This was a two-part, single-center, single-blind study in non-dependent, recreational opioid abusers with experience in nasal snorting (Figure 13).

In Part 1 of the study, the maximum tolerated, intranasal dose of crushed Acurox® Tablets was determined to be 2 x 7.5/30 mg tablets. In Part 2 of the study, subjects administered intranasal doses of: (1) the maximal dose of crushed Acurox® Tablets determined in Part 1; (2) a crushed 15 mg tablet of Roxicodone®; and (3) 15 mg of oxycodone powder. Doses were administered in random order, and separated by at least 6 days. All subjects received all doses.

Figure 13.   Study AP-ADF-106 Design
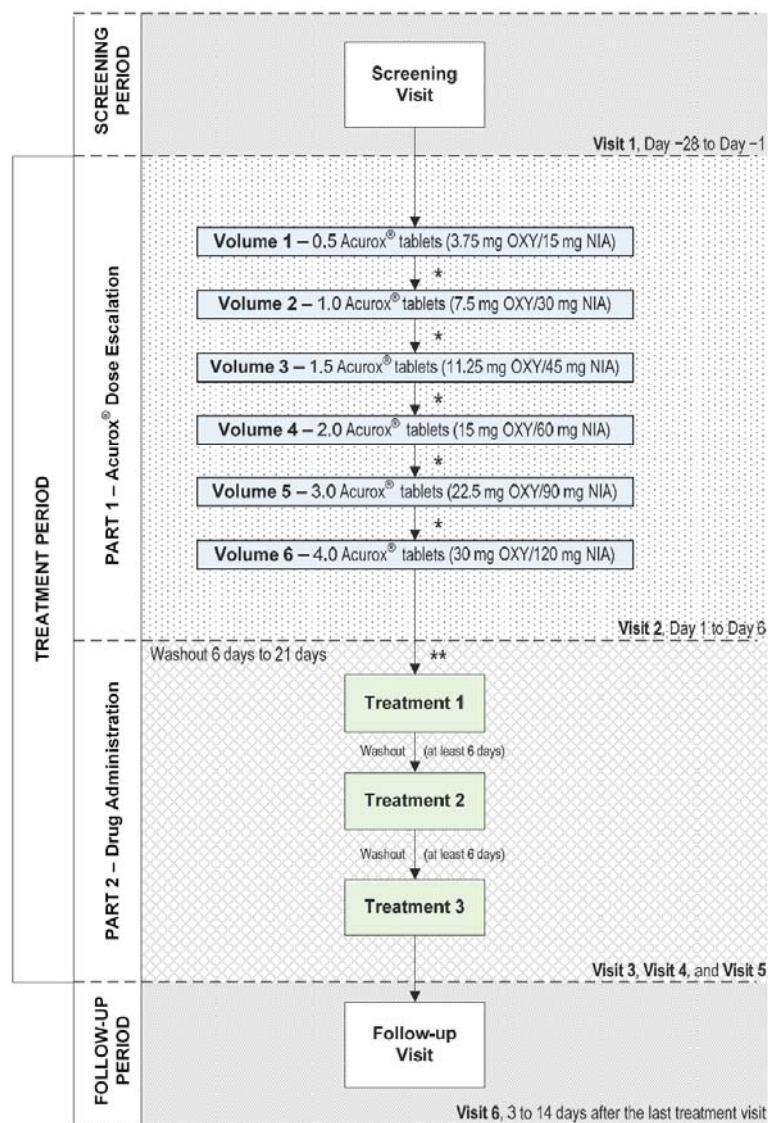
*   Study drug administration sessions were separated by approximately 24 hours. If at any point during the drug escalation procedure, a subject was unable or unwilling to complete the drug administration or if in the opinion of the investigator or designee it was not in a subject's best interest to continue, the dose escalation for the subject was stopped.

** During Part 2, subjects intranasally administered in randomized crossover one of three treatments (one per visit): (1) crushed Acurox® Tablets (7.5 mg oxycodone HCl/30 mg niacin); (2) crushed Roxicodone® tablets (15 mg oxycodone HCl tablets USP); or (3) oxycodone HCl powder. The dose of oxycodone HCl administered in Part 2 was the group median highest tolerated oxycodone HCl dose identified during Part 1.

Primary outcome measures used in Part 2 to assess abuse liability were: (1) Drug Liking/Disliking (at the moment and overall drug liking); (2) Overall Drug Effect; and (3) Take Drug Again Assessment.

Visual analog scales were utilized to score the subject's drug administration experience. Drug Liking/Disliking was assessed with a bipolar scale with possible scores ranging from 0 (meaning "strong disliking") to 100 ("strong liking"). Overall Drug Effect was assessed with a bipolar scale with possible scores ranging from 0 (meaning "very bad") to 100 ("very good"). For analysis purposes, a VAS score of 50 was considered neutral for the bipolar scales. The "Take Drug Again" question was assessed using a 0- to 100-point unipolar scale ranging from "definitely no" to "definitely yes."

Results

In Part 1 of the study, the maximum, tolerated, intranasal dose of crushed Acruox® Tablets was determined to be two 7.5/30 mg tablets. Fifteen subjects were enrolled, and 13 of 15 subjects completed Part 1. Two subjects were withdrawn: 1 subject did not completely administer the study drug and 1 subject was withdrawn due to an adverse event (headache of moderate intensity). Fourteen of the 15 subjects were included in the pharmacodynamic analyses for Part 1.

Fifteen subjects were enrolled in Part 2 of the study. This included 13 subjects who completed Part 1 and two replacement subjects. Twelve of these 15 subjects completed Part 2. Two subjects were excluded from the pharmacodynamic and pharmacokinetic analyses. One did not complete study drug administration in one dosing session, and one subject was excluded for a major protocol violation in dispensing. Therefore, 10 subjects remained to be included in the pharmacodynamic and pharmacokinetic analyses.

As illustrated in Figure 14, the mean "at the moment" VAS scores for subject-rated Drug Liking for crushed Acurox® Tablets was associated with an initial dislike of the drug (score of 44.7 at 0.5 hours post dose) followed by an increase to neutral or slight liking score for the remainder of the assessment period (scores ranging from 47.1 to 55.0). By contrast, administration of crushed Roxicodone® tablets and oxycodone HCl powder were associated with a sharp spike in liking scores, peaking at 0.5 hour post dose (scores of 87.4 and 83.0, respectively) followed by a gradual decline in liking scores (to 56.8 and 61.6, respectively).

Importantly, intranasal administration of crushed Acurox® Tablets caused significantly greater aversive objective effects (for nasal congestion and irritation [peak effect and AUE_{0-2h}], $p \leq 0.0223$) and aversive subjective effects (for nasal burning, congestion and need to blow nose [peak effect and AUE_{0-2h}], $p \leq 0.0038$) compared to intranasal administration of the same oxycodone HCl dose in crushed Roxicodone® tablets and oxycodone HCl powder. Among a multitude of aversive effects, intranasal administration of crushed Acurox® Tablets caused significantly more nasal burning compared to Roxicodone® ($p \leq 0.0066$) and oxycodone HCl powder ($p \leq 0.0068$). No significant differences were found in objective and subjective effects between crushed Roxicodone® tablets and oxycodone HCl powder.

Figure 14.   Study AP-ADF-106 Drug Liking VAS Scores "At the Moment": Part 2
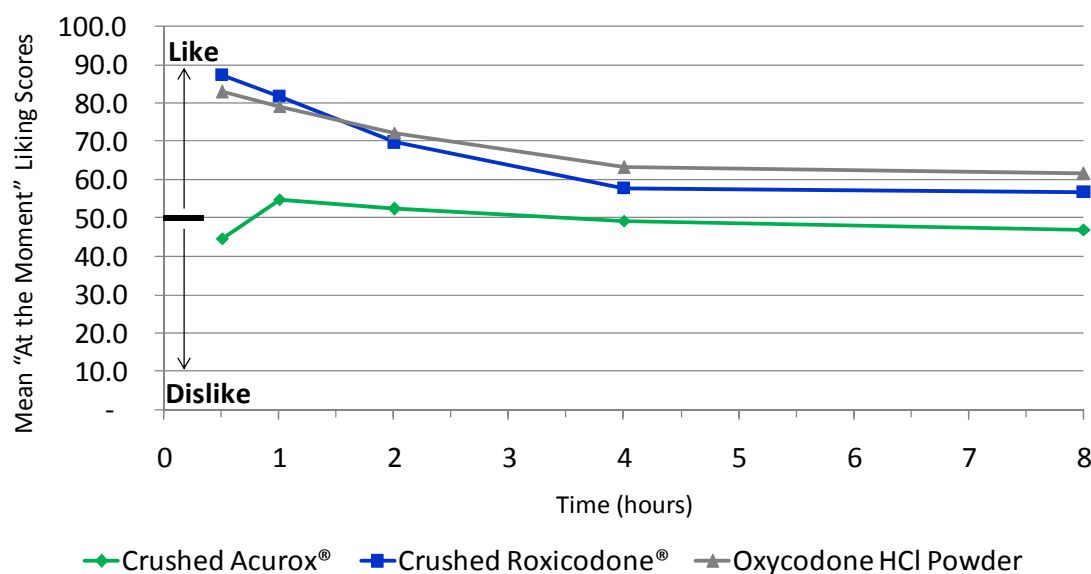
Figure 15, Figure 16, and Figure 17 illustrate the mean VAS Overall subject rated assessments for Drug Experience, Drug Liking and Take Drug Again, respectively. The p-values in these figures relate to the maximum peak effect experienced by subjects from crushed Roxicodone® Tablets and oxycodone HCl powder compared to crushed Acurox® Tablets.

Figure 15.   Study AP-ADF-106 Overall Drug Experience Mean VAS Scores: Part 2
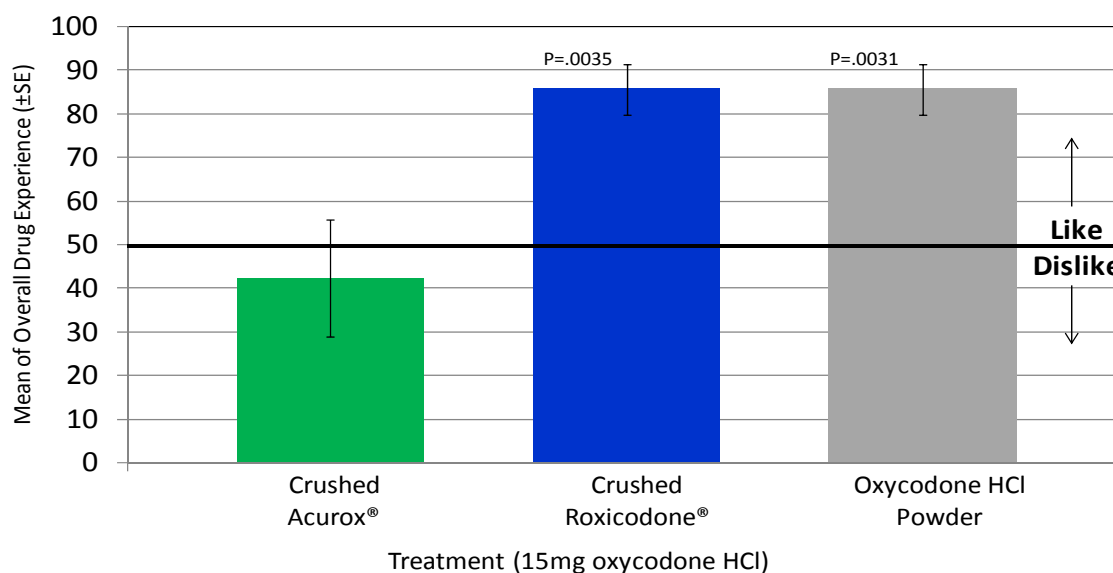
P-values = Emax for Acurox vs. comparator treatments

Figure 16.   Study AP-ADF-106 Overall Drug Liking Mean VAS Scores: Part 2

P-values = Emax for Acurox vs. comparator treatments

Figure 17.   Study AP-ADF-106 Take Drug Again Mean VAS Scores: Part 2

Take Drug Again Scores could range from:
"0" (would definitely not take again) to
"100" (would definitely take again)

P-values = Emax for Acurox vs. comparator treatments

Table 9.   Study AP-ADF-106 Overall Subject Rated Assessments: Part 2

VAS Scores: Overall Subject-Rated Assessments

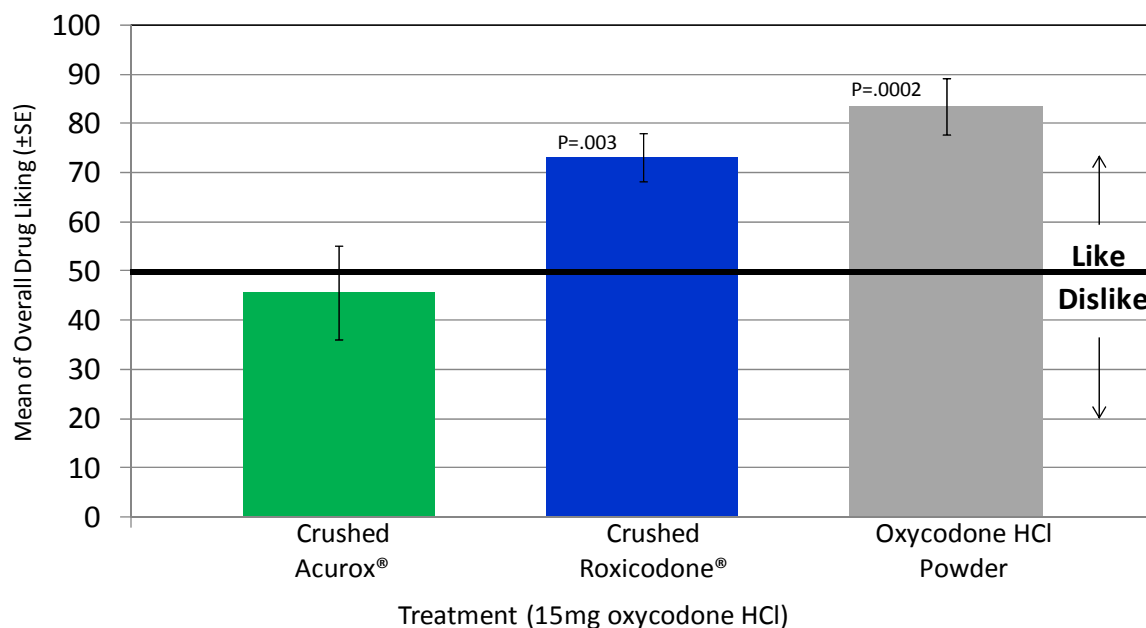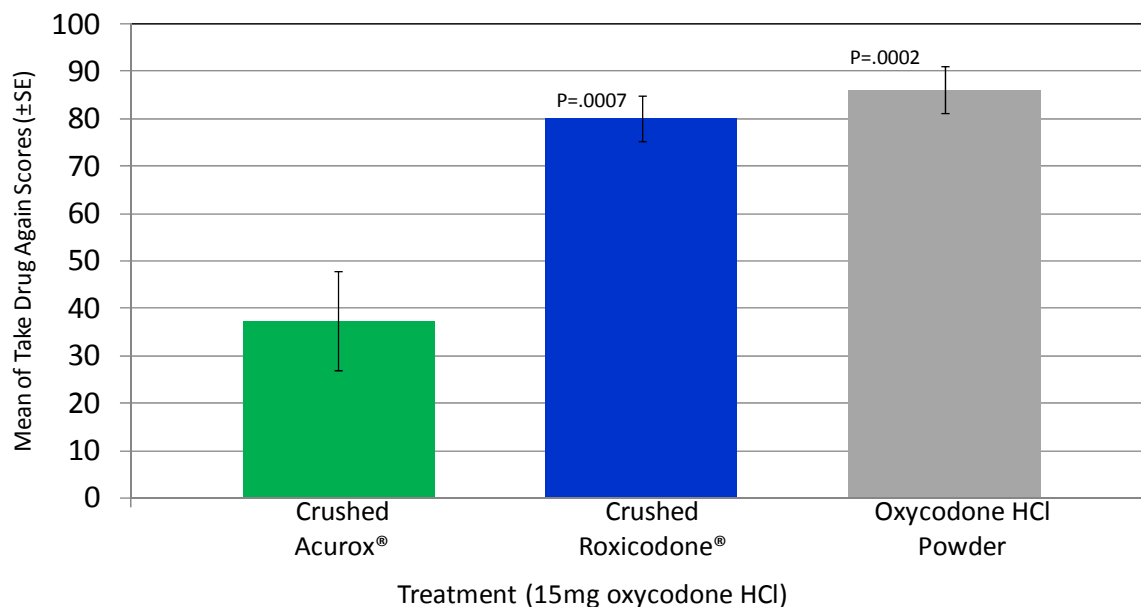| Assessment	Crushed Acurox®	Crushed Roxicodone®	Oxycodone HCl Powder
Overall Drug Experience			
Mean (SD)	42.2 (42.67)	85.6 (18.36)	85.6 (18.45)
Range	0 – 100	46 – 100	50 – 100
Overall Drug Liking			
Mean (SD)	45.6 (30.40)	73.1 (15.82)	83.5 (17.89)
Range	0 – 100	50 – 100	50 - 100
Take Drug Again			
Mean (SD)	37.3 (32.88)	80.0 (15.29)	86.0 (15.72)
Range	0 - 100	56 – 100	61 – 100

As illustrated in Figure 16 and Table 9, mean Overall Drug Liking for crushed Acurox® Tablets was below the neutral level (i.e., <50) suggesting a dislike for 2 crushed Acurox® Tablets. In contrast, the mean Overall Drug Liking for Roxicodone® and oxycodone HCl powder (73.1 and 83.5, respectively) were well above the neutral level, suggesting a relatively strong liking effect. In this study, subjects clearly preferred the crushed Roxicodone® and oxycodone HCl powder to crushed Acurox® Tablets. This was confirmed using analysis of variance, which showed significant differences between crushed Acurox® Tablets and crushed Roxicodone® (p = 0.003) and between crushed Acurox® Tablets and oxycodone HCl powder (p = 0.0002). In contrast, differences between the crushed Roxicodone® Tablet and oxycodone HCl powder were not significant (p = 0.1342). These results were further confirmed with mean analysis of the Overall Drug Experience scores (Figure 15 and Table 9) and Take Drug Again scores (Figure 17 and Table 9) exhibiting similar results. Across several measures, these results consistently show that Acurox® Tablets were disliked compared to oxycodone HCl powder and crushed Roxicodone® taken intranasally.

Conclusions

The subjects indicated that they preferred crushed Roxicodone® Tablets and oxycodone HCl powder over Acurox® Tablets, and importantly that they would not take crushed Acurox® Tablets again but would take the crushed Roxicodone® Tablet and oxycodone HCl powder again. This is a demonstration that a relative dislike for one preparation over another may well be associated with a change in drug-taking behavior. It is therefore reasonable to conclude that intranasal administration of 2 crushed Acurox® Tablets 7.5/30 mg has a substantially lower potential for abuse than the same oxycodone HCl dose administered as crushed Roxicodone® tablets and oxycodone HCl powder. Acurox® Tablets have the potential to deter abuse by the intranasal route.

6.2.3   *Evidence Supporting Intravenous Abuse Deterrence*

6.2.3.1   In Vitro Extraction Tests

The Extraction Test evaluated the relative difficulty with which Acurox® Tablets could be dissolved to provide oxycodone for IV use. A leading independent laboratory was contracted for this test, in which professional chemists were instructed to use any methodology, solvent, and equipment of their choosing to extract oxycodone from the tablets in a form and volume suitable for IV injection. Acurox® Tablets were provided to the laboratory, along with 3 other currently marketed oxycodone HCl tablet formulations for comparison: OxyContin® (oxycodone HCl) Controlled-Release Tablets, generic oxycodone HCl Tablets, and Percocet® (oxycodone HCl/acetaminophen) Tablets. Data from the Extraction Test showed that the currently marketed oxycodone-containing tablets were easily dissolved in water for potential abuse by IV injection in as little as 3 to 10 minutes. In contrast, the data showed that preparing an injectable form of Acurox® Tablets was difficult and impractical due to the time required and the inability to obtain a sufficient oxycodone yield that would provide any degree of euphoric effect to the prospective drug abuser.

6.2.3.2   In Vitro Syringeability Tests

The Syringe Test was developed by Acura Pharmaceuticals to assess the difficulty with which a solution made from dissolved Acurox® Tablets could be drawn into a syringe for IV injection. A variety of commercially available solvents was used to dissolve crushed Acurox® Tablets. The resulting solution was then drawn into a syringe; the amount of solution drawn was measured and the difficulty of drawing the solution was rated as "not possible to inject," "not likely to be injected," and "theoretically injectable." The Syringe Test results suggested that preparing an injectable form of Acurox® Tablets using a wide variety of available solvents is impractical due to high solvent volume requirements and the viscous/gelatinous mixture that results from dissolving the tablets in lower volumes of the solvents tested. Even solutions rated "theoretically injectable" would require further processing by the prospective abuser to separate oxycodone from other tablet ingredients (including niacin and numerous excipients) and reduce the total volume to provide a solution in a form and volume that is practically suitable for IV injection.

Conclusions

The Syringe Test simulates the physical difficulty and quantifies the approximate solvent volume required using various potential injectable solvents and crushed Acurox® Tablets to achieve a Theoretically Injectable IV solution. The Syringe Test results suggest that preparing an injectable form of Acurox® Tablets using a variety of available solvents is impractical due to high solvent volume requirements and the viscous/gelatinous mixture formed when dissolving Acurox® Tablets in lower volumes of the solvents tested. With the Syringe Test, even a "Theoretically Injectable" solution of crushed Acurox® Tablets would require further processing by the prospective abuser to separate oxycodone from other tablet ingredients (including niacin and numerous excipients) and a reduction in total volume to provide a solution in a volume and form that is practically suitable for IV injection.

6.2.4   *Overall Abuse Liability Summary*

A broad range of laboratory and clinical studies (AP-ADF-102, AP-ADF-106, AP-ADF-111, AP-ADF-114, Extraction Test, and Syringe Test) were conducted evaluating the potential for abuse of Acurox® Tablets. These studies were designed to simulate common methods of opioid analgesic tablet abuse and to provide insight into potential behavior of prospective opioid abusers in the "real-world" community.

Despite certain limitations of laboratory and clinical studies, the results of these studies consistently demonstrate that Acurox® Tablets possess decreased likelihood or potential for abuse compared to currently approved and marketed oxycodone-containing tablet products. The conclusions from these studies are summarized below:

6.2.4.1   Abuse Liability Related to Oral Swallowing of Excess Numbers of Tablets

Well-designed, double-blind clinical studies with a variety of methodologies in non-dependent recreational opioid drug abusers have demonstrated that Acurox® Tablets swallowed in oral doses in excess of the proposed recommended doses were significantly disliked compared to equivalent doses of oxycodone HCl alone (without niacin) 30 minutes after oral ingestion and before the peak liking effect of oxycodone. Furthermore, the disliking caused by niacin in these studies was reinforced by the global assessments of Take Drug Again Assessment (TDAA) or the Treatment Enjoyment Assessment Questionnaire (TEAQ). When given a choice, these recreational drug abusers significantly preferred to take oxycodone HCl tablets without niacin again compared to Acurox® Tablets. The TDAA/TEAQ are surrogate measures validated in clinical abuse liability studies and predictive of potential abuse of a drug but not yet correlated to the real-world environment. Excess oral doses of Acurox® Tablets caused significant disliking and bodily discomfort compared to oxycodone HCl tablets alone (without niacin). These studies provide substantial evidence that Acurox® Tablets have a lower abuse potential than oxycodone HCl tablets when excess oral doses are swallowed, and therefore have the potential to limit or impede this common form of misuse and abuse.

Niacin-induced disliking of oxycodone may be attenuated by food. At the same time, however, there is evidence to suggest that food may also attenuate "drug liking" and may delay the time to achieve maximum "drug liking;" both of these effects would reduce the appeal of excess oral doses of Acurox® Tablets for recreational use or abuse.

Pre-medication with an NSAID 30 minutes or more before ingesting Acurox® may help mitigate the niacin-induced flushing associated with excessive oral intake of Acurox® Tablets but this behavior would be contrary to an abuser's usual drug-taking practices. Furthermore, as explained in Section 5.5.2, NSAIDs do not completely mitigate flushing.

As discussed in Section 5.2, tolerance to niacin may develop over one or more weeks of uninterrupted use. However, a patient who stops taking niacin for several days will have the flushing response restored when a subsequent dose of niacin is taken. Furthermore, if the dose of niacin is increased in a "tolerant" patient, the flushing response returns. This is an important consideration for people who misuse or abuse opioids and who are on other sources of niacin (e.g., to food supplements or for treating lipid disorders), or who may be on a stable dose of Acurox® Tablets and then increase their dose above the proposed

recommended dose for pain. As the dose of niacin is increased, disliking effects of niacin will be restored.

6.2.4.2   Abuse Liability Related to Nasal Administration of Crushed Tablets

A well-designed, single-blind, two-part clinical study among known non-dependent recreational opioid drug abusers with experience in nasal snorting has demonstrated that crushed oxycodone HCl tablets and oxycodone HCl powder (both at a dose of 15 mg oxycodone) are liked significantly more than the 15 mg of oxycodone HCl contained in 2 crushed Acurox® Tablets 7.5/30 mg. These results were consistent across several measures. The occurrence of AEs related to nasal irritation support that snorting Acurox® Tablets is associated with disliking effects. Furthermore, these recreational drug abusers were significantly less willing to snort crushed Acurox® Tablets again compared to crushed oxycodone HCl tablets and oxycodone HCl powder. This two-part clinical study provides substantial evidence suggesting that Acurox® Tablets have a lower potential for abuse than oxycodone tablets (without niacin) and pure oxycodone HCl powder when these products are nasally administered.

6.2.4.3   Abuse Liability Related to IV Injection of Dissolved Tablets

Two laboratory studies (the Extraction Test and the Syringe Test) were conducted to evaluate abuse liability related to IV administration of oxycodone obtained from dissolved or chemically altered Acurox® Tablets. In the Extraction Test it was determined by an independent third party laboratory that extracting oxycodone from a tablet in a form and volume suitable for IV administration was substantially more difficult and time consuming for Acurox® Tablets compared to 3 widely prescribed and currently marketed tablet products containing oxycodone. In the Syringe Test it was determined, using numerous solvents suitable for IV injection, that large volumes of solvent are required to sufficiently dissolve Acurox® Tablets to the extent that the resulting solution can theoretically be withdrawn into a needle and syringe for IV injection. The Extraction Test and the Syringe Test provide substantial evidence suggesting that Acurox® Tablets may have a reduced potential for abuse for IV injection compared to currently available oxycodone-containing tablet products.

6.2.5   Abuse Liability Conclusions

Acurox® Tablets provide clinically meaningful and statistically significant benefits over current commercially available IR oxycodone HCl tablets in potentially limiting or impeding oral, intranasal, and intravenous abuse of the oxycodone (analgesic) component of the product. Importantly, Acurox® Tablets provide the following benefits:

Novice, Experimenter

Acurox® Tablets have the potential, through niacin induced disliking, to impact oral abuse behavior patterns and perhaps limit dose escalation experimentation and thereby reduce overdose and death in this often young and naïve population of new initiates. In addition, the Aversion® Technology platform used in Acurox® Tablets has the potential to discourage progression to other routes of abuse such as snorting.

Established, Non-dependent

Acurox® Tablets have the potential to reduce addiction, overdose, and death even in this experienced population by impacting oral and nasal abuse behavior patterns. The dose of niacin in Acurox® Tablets that would be ingested with escalating doses of oxycodone, and niacin's aversive effects at these doses may help to prevent overdose and death in some people. The Aversion® Technology platform has the potential to deter progression to snorting as this method is less liked by abusers as well. Finally, Acurox® Tablets may discourage or even prevent these abusers from progressing to IV use.

Dependent Addict

Importantly for this population, Acurox® Tablets have demonstrated the ability to resist extraction and IV administration, a dangerous route of administration and one that is associated with transmission of disease. This population is most challenging as they require opioid maintenance to avoid withdrawal. They are more likely to tolerate or perhaps mitigate the mechanisms of Acurox® Tablets.

Abuse liability studies can only generate surrogate measures intended to predict the impact on the relative misuse or abuse rates in a real-world setting. Data to demonstrate actual changes in rates of misuse and abuse can only be collected in a post-approval setting by documenting an actual reduction in abuse and misuse of Acurox® Tablets relative to a comparator or comparators through longitudinal epidemiological studies.

Working with the Agency, a comprehensive post-approval surveillance program will be established for Acurox® Tablets to proactively monitor the abuse liability potential of Acurox® Tablets in clinical practice. This program will be multi-dimensional and will likely include using: (1) established databases such as RADARS® and ASI-MV® Connect, (2) focus groups with prescribers and insurance claim studies to evaluate prescription use patterns, (3) supportive surveys in college students and pain patients, and (4) prescriber and patient educational services on Acurox® and IR opioid abuse, misuse, and diversion. To our knowledge, such a program has never been performed with an IR opioid analgesic, and Acura and King Pharmaceuticals, Inc. are committed to such monitoring to begin to address the societal burden of IR opioid misuse and abuse.

7.   BENEFIT/RISK DISCUSSION AND CONCLUSIONS

Acurox® Tablets were developed as a combination drug product to be a safe, well tolerated, and effective IR opioid analgesic with the added ability to reduce the potential for opioid abuse. For abuse-deterrent opioids the assessment includes both the patients treated for pain, the target or intended population, and the individuals who use these products for non-medical purposes. Specifically the development of Acurox® focused on the 3 most common methods of misuse and abuse for IR opioids: oral, intranasal, and intravenous administration.

For products like Acurox®, which are intended to limit or impede abuse, the primary incremental benefit is a societal one demonstrated by a reduction in harmful events related to potential misuse and abuse. This benefit pertains to both patients and non-patients.

The Sponsor acknowledges that the benefits of niacin in Acurox® Tablets in limiting or impeding oral abuse of IR oxycodone are not perfect, and may be mitigated to varying degrees through abuser knowledge and planning by co-administration with food or an NSAID. However, as discussed in this Briefing Document, this mitigation does not occur in all circumstances. In addition, food also adversely affects the pharmacokinetics of oxycodone by delaying time to peak effect and lowering mean drug liking. NSAIDs have shown variable responses to mitigating niacin induced flushing that could depend on dose, timing, and type of NSAID taken. There is likely to be a subset of abusers (naïve, new high school or college initiates) in which pre-planning will not occur, or drug interaction knowledge be known.

Benefit/Risk to the Intended Population

Acurox® Tablets provide an abuse deterrent formulation combining an existing approved drug (oxycodone HCl) to treat pain, and a second approved drug (niacin) to reduce the potential of abuse of oxycodone HCl. The incremental risk to the target pain population is the incremental risk associated with niacin.

In the intended population using Acurox® Tablets as prescribed, the risks compared to placebo were assessed in a pivotal safety and efficacy study. Study 105 demonstrated the analgesic efficacy of proposed recommended doses of Acurox® Tablets in patients with moderate to severe pain. The risks to patients in this population are the typical risks of opioid therapy, and an incremental risk associated with a 10-15% higher incidence of mild to moderate flushing compared to placebo. However, niacin induced flushing did not affect the analgesic efficacy of Acurox® Tablets or result in patients discontinuing from the study. Niacin has an extensively demonstrated safety record at much higher doses observed in chronic use clinical trials and through decades of clinical use. Flushing, if it manifests at a 60 mg dose of niacin in a subset of the intended population, is a mild and benign effect that can be easily managed through appropriate product labeling.

Benefit/Risk to Unintended Populations of Abusers and Misusers

Patients misusing their prescription of Acurox® Tablets may be discouraged from excess oral consumption by the disliking effects induced by niacin. The unintended population for use of Acurox® Tablets includes various categories of potential opioid abusers. New users and those

experimenting, often high school and college students, may be discouraged by the disliking effects induced by swallowing oral excess doses of Acurox®. This also has the potential for discouraging this population from progressing to even higher and potentially more hazardous doses of oxycodone. In addition, Acurox® has the potential to deter progression of this group to other routes of abuse such as snorting.

In the established non-dependent opioid abusers, the oral and nasal routes of administration are more common. Likability of the opioid is a priority to this group. Reinforcement increases the oxycodone dose requirements in these individuals. The dose of niacin in Acurox® Tablets that would be ingested with escalating doses of oxycodone, and niacin's aversive effects at these doses may help to prevent overdose and death in some people. The Aversion Technology® platform has the potential to deter progression to snorting. In either case, Acurox® Tablets may help prevent morbidity and mortality or deter progression in some individuals.

In hard-core abusers and addicts, physical and chemical manipulation, extractability, and likeability are key components. Acurox® Tablets were developed to limit or impede the oral, intranasal, and intravenous routes of abuse so prevalent in this population. The obstacles to abuse in the composition of Acurox® may cause abusers, drug diverters and dealers to seek more desirable abuseable drugs.

Niacin is intended to deter abuse by inducing disliking in individuals who take excess doses of Acurox®. Whereas these individuals are at risk of the well recognized harmful effects of high doses of oxycodone, there is no evidence that the niacin dose in Acurox® to achieve these high doses of oxycodone is anything other than a clinically benign cutaneous phenomenon. Niacin therefore contributes to a minimal incremental risk in the abuser populations.

Conclusions

The individual and societal consequences of prescription opioid abuse in America are substantial.

Acurox® Tablets provide incremental benefits over current commercially available IR oxycodone HCl tablets in potentially limiting or impeding abusive behaviors in the abuse populations of concern across the three common routes of administration. Importantly, this incremental benefit includes the introduction of limits or impediments to oral abuse by the presence of niacin in the medicine. These benefits are provided without incurring an incremental safety penalty to either the intended pain population, or the unintended abuser populations. It is not a perfect solution to the opioid abuse crisis, but it is a solution that warrants approval of the product.

The incremental improvement in the potential to deter abuse when compared to available IR opioids is likely to be associated with a public health benefit once Acurox® Tablets is approved and used in routine clinical practice.

To further ensure that benefits outweigh risks, a comprehensive post-approval surveillance program will be established for Acurox® Tablets to proactively monitor in clinical practice the rates of misuse and abuse of Acurox® Tablets relative to other IR opioids. This program will be multi-dimensional and involve: (1) established government and proprietary databases such as RADARS® and ASI-MV® Connect; (2) focus groups with prescribers and insurance

claim studies to evaluate prescription use patterns; (3) supportive surveys in college students and pain patients; and (4) prescriber and patient educational services on Acurox® and IR opioid abuse, misuse, and diversion. To our knowledge, such a program has never been performed with an IR opioid analgesic.

Prescribers, patients, and dispensers will be educated on the possibility of flushing occurring at recommended doses. This will be accomplished through appropriate product labeling. Monitoring and surveillance of flushing and other AEs will be performed using both passive and active approaches, as well as patient surveys. Interventions will be based on periodic situation analysis of surveillance data.

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